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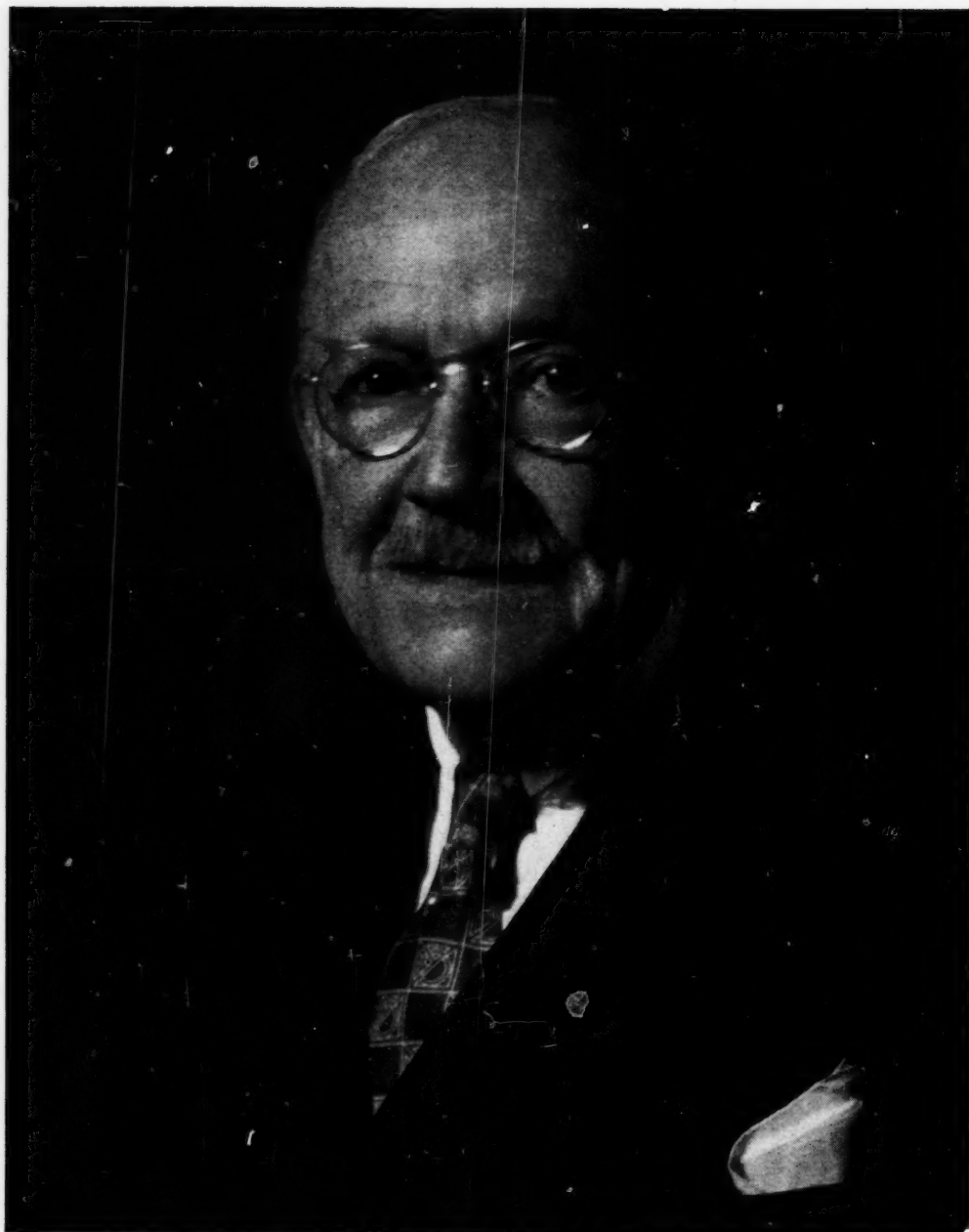
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DR. GEORGE W. KOSMAK

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## INTRODUCTION TO THE FESTSCHRIFT FOR DR. GEORGE W. KOSMAK

**A** YEAR ago the Editors of THE JOURNAL wrote briefly in celebration of Dr. George Kosmak's eightieth birthday and promised within a year to publish a Festschrift in his honor. The present special number is the result.

Over a year has been spent in preparation. Invitations to contribute were sent to a number of Dr. Kosmak's friends, to the members of the Editorial and Policy Committees of the JOURNAL, and to other leaders both here and abroad. The response has been far beyond our expectations so that a number of unusual size has been required to publish all of the material.

Some effort was made to seek special subject matter and with some invitations went requests for manuscripts on particular topics. In general, however, contributors have written on what they wished. Nevertheless, the manuscripts which have been received seem to the Editors to give a broad picture of what obstetrics and gynecology has accomplished in the last twenty-five years and what it has become today.

Obstetrics and gynecology, like others of the great branches of medicine, is no longer a simple medical specialty. It is becoming a federation of skills and particular areas of knowledge, a constellation of specialties. At its center is a large nucleus of clinicians, carrying on an enormous burden of precise and sometimes routine work that must be expertly performed and which is now constantly checked by increasingly prevalent statistical devices. Society, as well as our own organization, insists that this daily work be performed as expertly as present knowledge permits.

As available knowledge has been translated into established clinical procedure, stages are repeatedly arrived at where the need for new knowledge becomes apparent. Special areas, sterility, endocrinology, fetal physiology, and a dozen others have become permanently or temporarily segregated for special attention. Certain members of our specialty limit their activities to attain particular skills and carry on research in small areas. Calls for assistance go out to scientists in other fields, genetics, biochemistry, psychiatry, even sociology.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

A field of a greater obstetrics and gynecology is thus indistinctly outlined, outside of the scope of our daily work and much beyond the capacities of any single individual.

What then serves to define obstetrics and gynecology, to give its outline sufficient tangibility so that it can be easily conceived of? The field is not held together by instruments or apparatus peculiar to it, as is true of some specialties, nor by the anatomical or physiological problems of an unusually difficult surgical region. The technical intricacies of obstetrics and gynecology are not great and the general practitioner does most of the deliveries and the general surgeons, perhaps, most of the hysterectomies of the country. Our specialty has to hold it together only a concept, that of responsibility for the medical problems of the female patient arising in relation to the function of procreation, for the fetus during intrauterine life, for the newborn during the early neonatal period, as well as for the woman before and after the menopause. The specialty is then characterized by an inclusive idea, which provides romance and inspiration, but, probably fortunately, no complete bar to the participation in the work of those who are not formal specialists.

With this perhaps too philosophical introduction, the Editors offer the contributions to The Kosmak Festschrift as a sort of panorama of modern obstetrics and gynecology. The articles have been arranged in a rough pattern which describes what appears to us to have been the major organizational influences shaping obstetrics and gynecology in the last quarter of a century and which illustrates the major fields in which work has been done to expand knowledge or to improve clinical performance.

It has seemed most appropriate to select for the introduction to Dr. Kosmak's Festschrift "Thoughts on Editing a Journal of Obstetrics and Gynecology" by the distinguished editor of the British *Journal*. At this point it may be noted that one of the characteristics of the last quarter century of obstetrics and gynecology has been the intensification of writing in the field. The AMERICAN JOURNAL has nearly doubled the number of pages devoted each month to scientific material and we have welcomed, as rivals and collaborators, several new publications, the *Obstetrical and Gynecological Survey*, *Obstetrics and Gynecology*, and others. It seems safe to estimate that six times as much material is being published in the United States on obstetrics and gynecology as in the days of the founding of this JOURNAL. One is filled with some dismay at the thought of possible further progress in this respect.

Organizational developments of the last twenty-five years have been of surpassing importance in determining the evolution of obstetrics and gynecology. The idea of the combined specialty, brought to its culmination in Central Europe many years ago, has shown slow, if steady, progress in the United States, held back perhaps by the tradition of diversity in American medical educational institutions. As a measure to establish minimum and to raise average standards, the American Board has had a pervading influence. Finally, the maternal mortality committees, begun almost simultaneously in several American communities, have spread over the country to become constant guardians of obstetrical practice.



Partly as a result of the activities of the committees on maternal mortality, the obstetrician, and only to a lesser degree the gynecologist, have developed a susceptibility to statistics and their work and thinking have become deeply tinged with public health attitudes. Institutions and communities have become highly sensitive to figures on maternal and fetal mortality. Evidence is plentiful that these data are not only an American preoccupation but are recognized through many parts of the world as one of the best objective gauges of the level of social organization.

Within this broad setting, and perhaps to some extent in conscious reaction to it, the medicine of obstetrics and gynecology has entered a period of rapid scientific development. This has occurred in a number of partly independent, but fundamentally related, fields.

Studies on ovulation, conception, and the implantation of the ovum have cast a light on phases of human development unknown a few years ago. Similarly, fetal physiology, long apparently regarded as inaccessible, has become a subject of study, both for itself and as a hoped-for avenue to the prevention of many congenital defects or intrauterine accidents. That this is a field in which the clinician may soon exercise increasing influence and carry increasing responsibility seems nearly assured.

The effects of gestation on the mother have given rise to the concept of "maternal physiology," which in its applied aspects is contributing to the better care of women with pregnancy complicated by constitutional illness, especially by cardiovascular disease, and has led directly to a more rational study of toxemia of pregnancy. Although the cause of this disease and a specific for its therapy have not yet been found, present methods seem to point the way to their discovery. In spite of a greater degree of specialization the obstetrician is a better physician than he was a generation ago.

The management of labor itself has been revolutionized. This has been chiefly the result of careful antepartum studies, including the precise measurement of pelvic capacity and the emergence of cesarean section as a safe procedure. The consequence has been a measure of standardization of procedure and to some extent a reduction in the range of the obstetrician's repertory of operations. Controversy persists as to the proper frequency of cesarean section and assumes some metaphysical aspects when there are considered the not necessarily mutually exclusive claims of anesthesia and natural childbirth. Obstetrics has become less dramatic and less sanguineous, more routine and more scientific.

A great extension in the understanding of the functional disorders of gynecology also took place in this era. It began perhaps with the careful correlation of histologic change in ovary and endometrium with clinical symptoms. To this pair of interrelated phenomena a third was added, the behavior of the chemical products of the endocrine glands, particularly of the ovary and pituitary. Though much has been done, the systematic mapping of these clinical, morphological, and chemical relationships remains incomplete.

Gynecologic pathology, although its fundamentals have been well known for many years, has remained a field close to the clinician and one which the clinically trained gynecologist has largely developed for himself. Recent years have witnessed a refinement in classification and diagnosis and an effort to connect more closely microscopic findings with clinical potentialities. For the future it seems a field that must be closely guarded lest its very familiarity tempt the gynecologist to let it pass from his hands into those of departments of general pathology where the work may be more efficiently performed but where the connection between clinical problems and the tools for their solution may become attenuated.

Gynecologic surgery, one must admit, gives signs of passing into the phase of a respectable, if not completely respected, old age. Pioneering in new principles seems nearly over. Problems of operative mortality have given place to studies in comparative morbidity. Techniques are less an issue than indications, both with the gynecologists and indeed with some onlookers among the laity. Yet the problem of the fitting of indications into the physiological and psychological life of the patient are as great an intellectual challenge, if less of an adventure, than any offered in the earliest days of the hysterectomy.

Only in the case of pelvic cancer has some of this adventure survived or perhaps temporarily returned. Yet this may be ephemeral, a kind of afterglow, for in our day it seems scarcely possible that the mechanical approach of the surgeon, even with the new surgical physiology, can keep pace forever with the apparently infinite promises of chemistry and physics. As of today, however, surgery and radiation both occupy the field, maintaining the excitement of their half century of competition, somewhat mitigated by the oft repeated and only partly true assertion that they are collaborators and not contestants.

The contributions to the Festschrift are thinly spread over this enormous field which gynecology and obstetrics has encompassed. They illustrate but do not comprehend the subject. Nevertheless, the Editors believe that this collection points to many of the milestones passed in the last quarter century, gives a general, if uneven, outline of the present, and indicates a few of the many problems that the specialty must face and solve in the not distant future.

Dr. George Kosmak published many of the original contributions which served to establish obstetrics and gynecology in its present position in modern medicine.

*The Editors*

## THOUGHTS ON EDITING A JOURNAL OF OBSTETRICS AND GYNECOLOGY

JAMES YOUNG, M.D.\*

I WELCOME this opportunity of joining with others in paying tribute to Dr. George Kosmak. To the obstetrical and gynecological world he is known as the directing genius and in large part the creator of one of the most influential journals in our specialty existing at the present time. To a smaller circle, in whom I venture to number myself, he is known as a trusted, generous, and warm-hearted friend.

I have been asked to write some thoughts inspired by my experience as a fellow editor.

The main function of such a journal as ours is the diffusion of knowledge and thus to contribute to the raising and maintenance of the standard of learning in the specialty. In so far as it provides the medium for the publication of new discoveries it has, in addition, an indirect but important function to play in the extension of knowledge. In performing these two functions it has some resemblance to the university or school. At the same time the didactic teaching which is native to the university is hardly suitable for a specialist journal. Here the didactic lecture is in general out of place. The basic content of the journal is the "original" article and it is of the essence of such an article that it should be original. Whether dealing with the study of a clinical condition, or a pathological lesion, or with experimental work, it must give evidence of a newness and freshness of approach and outlook.

Herein lies the difficulty for, while the journal has a wide open door for the record of some new method of investigation and treatment, of a new appraisal of clinical data or of pure research, the door is open only shyly to the record of routine clinical studies. The clinical article that rouses by its novelty of observation and emphasis will always find a warm welcome. But it is otherwise with the unimaginative catalogue of routine observations made in hospital or clinic. There is the article which is the bugbear of all editors, that built up on the belief that the study of 500 cases of any clinical state is bound to be fruitful. While an intensive study of ten cases may be rewarding, the study of 1,000 cases of the same condition is in its nature likely to be perfunctory and sterile. I remember hearing the great British cardiologist, Sir James Mackenzie, relate that, when he was called from his general practice to take charge of a research department of fifty beds in one of the large medical schools in London, he replied that he would gladly accept the offer but only on the understanding that the department was limited to fifteen beds.

\*Editor, *The Journal of Obstetrics and Gynaecology of the British Empire.*

Original articles vary greatly in their standard and in their value to the readers. While it is incumbent upon the editor to aim at the highest average standard, his judgment is often sorely tried when he receives a communication from a young writer which, although hardly reaching the desired level, yet shows evidence of sincere and promising work. Beginnings in their nature are likely to be immature and youth needs encouragement above all things. There is then for the editor the delicate question as to how far he is justified in making allowances for inexperience. It is, of course, generally accepted that the most suitable medium for such maiden efforts is the local society or journal. The young aspirant may seek guidance, and it is sometimes within the province of the editor to offer advice to such a beginner anxious to win his spurs, even to the extent of warning him against premature authorship and of discouraging him from the view that every clinical state that deviates slightly from the ordinary course is worthy of being nursed into publication.

While the publication of original articles is the chief function of a medical journal such as ours, it has other important activities. One of these relates to the part it should play as a clearinghouse for world literature. The policy to be adopted in this sphere has been the subject of much thought to those connected with the management of our *British Journal*. American obstetrics and gynecology is well served in this respect by the existence of journals and a *Year Book* concerned mainly with the critical abstracting of world literature, and, under Dr. Kosmak's editorship, the *AMERICAN JOURNAL* has covered the field in a commendable way in the Selected Abstracts which appear in each issue. In Great Britain we are less fortunate and we are worse off since the abstracting service of the British Medical Association has been so drastically curtailed.

I have long been convinced that the assembling of the worth-while literature of the world for its readers is one of the most rewarding enterprises that a medical journal can undertake. In these days of intense and multiple specialization, when so many branches of knowledge impinge on one's own limited field of study, the need for an adequate abstract service is greater than it has ever been. We have only to think of the many spheres in which discovery may have a major influence on our work—pediatrics, cardiology, hematology, endocrinology, radiology, radiotherapy, bacteriology, etc.—to realize the truth of this statement.

Those of us who have been concerned with the conduct of such an abstracting service know the difficulties that it has to contend with in a continuing degree. We know that some services in the past have succeeded for a time only, to succumb in the end to the growing administrative and financial trials. The recognition of these very real intrinsic difficulties, conjoined to the urgent need from a community standpoint that all advances in medicine should be made available at the earliest moment, has led some to the view that the direct and active encouragement of such services should become one of the health responsibilities of governments.

In the early days of medical journals there was a more intimate association between American and British medical publications than exists at the



present time. Thus I find that one of the earliest periodicals to appear in Britain, *Medical Essays and Observations*, founded by a society of physicians in Edinburgh in 1773, was reprinted wholesale in Philadelphia during the years 1773 to 1797. This journal, it is of interest to note, was the ancestor of *The Edinburgh Medical Journal*. The fourth volume of *The Memoirs of the Medical Society of London* (1790) contains a record of an operation for a full-time ectopic pregnancy carried out "by the late Dr. Charles McKnight of New York" from which the patient recovered. There is a note to the effect that this report was sent by Dr. James Mease of Philadelphia to Dr. Lettsom of London. When, at a later date, specialist journals appeared, the same close family relationship was maintained. Thus, *The Obstetrical Journal of Great Britain and Ireland*, founded in 1873 under the editorship of J. H. Aveling, had in each of its issues until the year 1879 a large *American Supplement*. The first supplement had an article by Dr. Albert H. Smith on "Clinical Observations on the Use of Pessaries in the Early Months of Pregnancy," as well as reports of the meetings of the Philadelphia Obstetrical Society, of the New York Academy of Medicine, and of the Boston Obstetric Society. The *British Gynaecological Journal*, founded in 1886 under the editorship of Fancourt Barnes, continued the same policy. The second volume contained a report of the Chicago Gynecological Society running to 45 pages!

Dr. Kosmak and I have discussed, but so far without result, the expediency of reviving this policy so happily followed by our predecessors. It can be claimed that in these days of multiple periodicals and rapid communication there is no clear need for such journalistic enterprise along these lines as existed in former times.

There are worries incidental to the editorial management of a journal. There are the authors who dally over their proofreading and there are those authors who want to rewrite a large part of their article after it has reached the proof stage. There are authors who write to say that they hope to have an article of considerable length ready within six months and would the editor be kind enough to reserve the appropriate space? There is even the author who submits an article of such length that it would occupy more than the space of one complete issue of the journal. But these are not matters which on the whole have caused me much anxiety. I have throughout my term of office come to appreciate the promptness in proofreading of the average contributor and the sacrifice of time and the public spirit of those who undertake the important task of reviewing books.

The routine work of the editor is sometimes relieved by the amusing interlude. Recently I found my editorial calm suddenly and unexpectedly disturbed by coming, in a sober article on the treatment of infertility, upon the account of a poor, sensitive woman, who, after long-deferred hope, decided to adopt a child. After months of preparation for the expected child, including a gradual month-by-month increase in her girth achieved by carefully concealed cushions, she announced to her neighbors that she was "going to a nursing home in a distant town to have her baby." After the appropriate



lapse of time she returned home with the infant and promptly became pregnant. The tragicomedy was completed by the arrival of the new infant prematurely at the end of the eighth month!

A short time ago one of our reviewers was greatly entertained by the quotations from Shakespeare placed as headings at the beginning of each of the chapters of a textbook on obstetrics. He was at a loss to know how to deal with this unusual innovation. He was lost in admiration at the remarkable aptness of the selected passages but at the same time he felt that they would be a dangerous example for others to follow. I quote some of the excerpts opposite their corresponding titles:

The Clinical Features of Normal Pregnancy	"O! how this mother swells up" ( <i>King Lear</i> )
The Management of Normal Pregnancy	"Your ladyship were best to have some guard about you" ( <i>Twelfth Night</i> )
The Toxaemias of Pregnancy	"My womb, my womb, my womb undoes me" ( <i>2 Henry IV</i> )
Uterine Bleeding During Early Pregnancy	"Retaining but a quantity of life, which bleeds away" ( <i>King John</i> )
The First Stage of Labour	"The mouth of the passage shall we fling wide ope" ( <i>King John</i> )
The Second Stage of Labour	"We'll put the matter to the present push" ( <i>Hamlet</i> )
The Third Stage of Labour	"Follow her close; give her good watch" ( <i>Hamlet</i> )

I would end these stray notes culled from the case book of a fellow editor by conveying to Dr. George Kosmak our congratulations on this memorable occasion and our appreciation of the JOURNAL which, for over thirty years under his charge, has upheld the high reputation of American obstetrics and gynecology and which has been greatly prized by many readers on this side of the Atlantic.

## THE COMBINED DEPARTMENTS OF OBSTETRICS AND GYNECOLOGY IN THE UNITED STATES

EDWARD A. SCHUMANN, M.D., PHILADELPHIA, PA.

OBSTETRICS by tradition is the second oldest specialty in medicine, it being readily conceded that the thoracotomy performed upon Adam gives surgery the senior rating. However, the phenomenon of the birth of Cain and Abel unquestionably gives obstetrics the second place.

Gynecology, on the other hand, is an extremely recent development in the field of medical specialties. Beginning with Ephraim McDowell and his ovariectomy in 1809, followed by the work of Marion Sims, Lawson Tate in England, and a host of successors to these pioneers, it was soon apparent that here was a fruitful and necessary division of medical effort.

In the early years there was no correlation whatsoever between the two departments, the obstetrician being a midwife and the gynecologist a general surgeon. As time passed the trend of obstetric technique became more definitely surgical. Paralleling this it was found so necessary for the gynecologist to have a full knowledge of obstetric injuries and the widespread lesions which might occur in the reproductive tract following abortion or delivery that the combination of the two became inevitable. The gynecologist became an obstetrician and the obstetrician became a gynecologist.

For the early history of the association of obstetrics and gynecology in American medical colleges I am indebted to Dr. James V. Ricci from whose book, *One Hundred Years of Gynecology*, the following extensive quotations are taken. Dr. Ricci states that some of the facts herein presented were obtained from *A System of Gynecology* by American authors edited by Matthew D. Mann in 1887.

"In 1818 the medical school of Castleton, Vermont, was the first to recognize diseases peculiar to women as a separate branch of instruction. Theodore Woodward (1788-1840), obstetrician, was designated to lecture on gynecology. Bowdoin College followed this example in 1825, and Dartmouth in 1838. As late as 1870 all of the professors of obstetrics in American medical institutions held the chair of gynecology and pediatrics. In that year, as the result of a memorial presented to the American Medical Association by the Boston Gynaecological Society, a resolution was passed recommending the establishment of a chair in gynaecology separate from obstetrics. Probably the first college to found a full professorship in gynaecology was Dartmouth, with E. R. Peaslee as the incumbent. In 1871, thirteen medical colleges in the United States had full professorships in gynaecology and obstetrics. Of this number, there were seven schools with full professorships in the diseases of women, with the incumbents teaching nothing else. These were: Albany

Medical College, with E. R. Peaslee; Long Island Hospital College, with A. J. C. Skene; St. Louis College of Physicians and Surgeons, with M. A. Pallen; University of Louisville, with T. Parvin; Medical College of Ohio, with C. D. Palmer; University of Pennsylvania, with William Goodell; and Detroit Medical College, with Edward W. Jenks."

"A general survey of the nineteenth century clearly shows that for the most part gynaecological therapy was medical. Too many professors in female disease abhorred surgery and wasted their talents on ineffectual drug therapy. However, by the middle of the century, three major surgical feats—the removal of an ovarian cyst, the repair of a vesico-vaginal fistula and the most infrequently successful hysterectomy for fibroids—had been performed by a few daring practitioners. These three successful operative measures slowly guided the profession into surgical channels, and were largely responsible for the new specialty—gynaecology."

"In some instances, the professor of abdominal surgery was also the professor of obstetrics. This association was short-lived since the association between obstetrics and gynaecology was increasingly evident. In the eighties, after centuries of being combined, pediatrics cast off its moorings and became a separate entity. This break was brought about mainly through the efforts of Abraham Jacobi of New York."

Since these early years the situation in the American medical schools is quite confused. In general it may be said that in the older schools separate chairs of obstetrics and gynecology are still maintained although in some instances they have been combined under the chairmanship of one or the other divisions and in almost all there has been at least some attempt at correlation of the two departments.

In the more recently established schools, notably the state universities, and, indeed, many privately endowed institutions, the chairs are generally combined and under the direction of one head. This movement was accelerated by the establishment of the American Board of Obstetrics and Gynecology in 1931, whose policy from the beginning was to insist upon training in both branches of the specialty and upon the granting of diplomas only to those men qualified in both obstetrics and gynecology.

In a few instances gynecology, while separate from obstetrics, is subordinate to the department of surgery but this division seems to be disappearing in most schools.

In the University of Pennsylvania, for example, there is a full professor of gynecology and one of obstetrics. Theoretically, these chairs are under one chairman and there is definite correlation in the appointment of residents and in the teaching program, the chairs, however, remaining entirely distinct. The same holds true of Harvard.

At Johns Hopkins, according to Dr. Richard W. TeLinde, the present professor of gynecology at that institution, the departments were combined in 1889, Dr. Howard A. Kelly being professor of gynecology and obstetrics. Dr. Kelly shortly divided the chair, arranging that Dr. J. Whitridge Williams should become professor of obstetrics. In 1911, the Hopkins placed the major

departments of the medical school under the full-time system which still exists. Upon the resignation of Dr. Kelly in 1919 the chair of gynecology was given to Dr. Thomas Cullen, but not as a major department, it being placed as a division of surgery. This arrangement continued until 1939 when Dr. TeLinde was appointed professor of gynecology and the department was again divorced from surgery and made independent, as it now is. At the present time there is close cooperation between the two departments and the five-year residency has been closely combined between the two professors.

At the Jefferson Medical College a somewhat similar condition prevails, the two departments being sovereign and independent but under the general chairmanship of the professor of gynecology. Here, too, there is close collaboration between the two divisions. Among the other larger Eastern schools, at Columbia, Yale, Cornell, Duke, North Carolina, Bowman Gray, Tufts, Temple University, and many others, the departments are wholly unified under one chief. This is also true of Louisiana State University. Throughout the Middle West and on the West Coast practically all of the schools possess fully combined departments. The same is true in Texas, Georgia, and other states. In general it may be said that the trend is steadily toward the combining of the two departments devoted to the diseases of women under one chairman who is usually in sole charge of the teaching program for both specialties.

As one examines the developments in the teaching of the two specialties it is both depressing and amusing to note the confusion and the feuds which marked this period. The ambition of certain professors of obstetrics to obtain control of gynecology without having the faintest conception of major operating technique was matched by the attempts of general surgery to eliminate gynecology as a specialty (this is still going on but without much success), and to relegate the teacher of obstetrics to his ancient role of midwife.

This whole delightful unreality and general disorder is well shown in the genealogy of obstetrics and gynecology at Tulane University. At this institution gynecology was first combined with obstetrics, subsequently became united with surgery, for some time was a separate chair, and is now again firmly combined with obstetrics. The same general principles hold true in the private and municipal hospitals of the country and, while some of the older ones still maintain separate departments, in the great majority obstetrics and gynecology are combined. In a very few institutions gynecology is not recognized as a specialty and pelvic surgery is performed in the general surgical department. In one well-known hospital until very recently even the cesarean sections were performed by the general surgeon but this situation is rapidly disappearing.

The history of the medical specialties is always fascinating, the struggles for recognition, followed sometimes by a certain aggrandizement of the specialist who wishes to extend his field unduly, and then a gradual reconciliation of differences and the assumption of its proper position in the medical field by each specialty.



## HISTORY OF THE NEW YORK ACADEMY OF MEDICINE COMMITTEE ON MATERNAL MORTALITY

BENJAMIN P. WATSON, M.D., LL.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Columbia University College of  
Physicians and Surgeons)*

THE advances made in scientific medicine over the past twenty years have probably been greater than in any similar period in medical history. The rapid and wide dissemination of a knowledge of these advances has led to their early adaptation to the needs of every branch of practice with a resulting saving of human lives. In no field has this been more spectacularly demonstrated than in that of obstetrics. In the year 1933 the maternal mortality rate in the United States was 61.9 per 10,000 live births. In the year 1950 it was 8.7 per 1,000 live births. Prior to 1930 the rate had not diminished but had rather shown a rising trend, 60.8 in 1915, 64.7 in 1925, and 67.3 in 1930.

The persistence of this high maternal mortality rate in the earlier years of the century in contrast to the progressive fall in the general mortality rate which was already well under way stimulated the interest of obstetricians in trying to find reasons for this discrepancy. Among those so interested and concerned was Dr. George W. Kosmak who, as a member of the Public Health Relations Committee of the New York Academy of Medicine, was familiar with the over-all picture and who, as a teacher and practitioner of obstetrics, realized that something must be wanting in the teaching and practice of his specialty. In 1917 he suggested to the Committee that it undertake a study of the subject. This it agreed to do and through a subcommittee distributed a questionnaire to all hospitals rendering obstetric service in New York City. The data obtained were found to be inadequate for the formulation of any definite conclusions and no report was issued. Ten years later another attempt to get at the facts surrounding maternal deaths was made by a study of the figures of the Bureau of Vital Statistics, but again without results. Nothing daunted, Dr. Kosmak persisted in his efforts so that in 1928 the Public Health Relations Committee deputed him along with the late Dr. Ralph W. Lobenstine to submit plans for "a study of the phases of the public health problems of obstetrics as they affect New York City." These plans were accepted and their implementation was entrusted to a subcommittee consisting of Dr. George W. Kosmak, the late Dr. John Polak, the late Dr. Henry Aranow, and Dr. Benjamin P. Watson, with Dr. Ransom S. Hooker as director of the study. Dr. Polak died during the course of the investigation and his place was taken by Dr. Charles A. Gordon.

The New York Obstetrical Society granted a loan for initial expenses and the Commonwealth Fund financed the work as it went along and also



the publication of the final report, entitled "Maternal Mortality in New York City. A Study of All Puerperal Deaths, 1930-1932."

The general plan as worked out by the Committee was to investigate every maternal death in the City of Greater New York over a three-year period beginning Jan. 1, 1930. The Registrar's office of the Department of Health agreed to furnish each week a photostatic copy of every death certificate which stated or implied a puerperal condition as the cause of death. Each case reported was investigated through a field staff of doctors and nurses. This investigation included an interview with the doctor in attendance, a survey of the hospital record, of the hospital facilities, and of home conditions. The questionnaire, based upon that used by Dr. Fred L. Adair and his colleagues in the "Fifteen States Study," aimed at getting every possible fact which might relate even remotely to the fatal outcome. As the tabulation of all these facts was completed each case was studied and discussed by the Committee without their having knowledge of the doctor or hospital concerned.

From the beginning an intensive effort was made to evaluate the data in relation to preventability or nonpreventability of the death and to come to some conclusion as to how the fatal result might have been averted. This plan of investigation was most important as affording the likeliest approach to the formulation of remedial measures. From the point of view of the members of the Committee it was the most exacting part of their work for it demanded a completely impersonal and objective approach to the consideration of each case. In holding the Committee to this concept Dr. Kosmak was a tower of strength.

When the final tabulations and calculations were made on the 2,041 maternal deaths in the three-year period it emerged that 1,343, or 65.8 per cent of them, had been classified as preventable and that in these the fault lay with the physician in 61.1 per cent, with the patient herself in 36.7 per cent, and with the midwife in 2.2 per cent.

It was foreseen by the director of the study, Dr. Ransom S. Hooker, by the members of the subcommittee, and by the Public Health Relations Committee of the New York Academy of Medicine that the publication of these figures would come as a great shock to the medical and lay public. These expectations were fully realized. The first reaction of a large body of physicians including general practitioners and obstetric specialists alike was one of indignation and a questioning of the validity of the conclusions arrived at. It was only after the report had been studied in detail and discussed in open meetings that calmer judgments prevailed and the profession realized that it was faced with a challenge. The challenge was quickly accepted with the result that throughout the country Maternal Welfare Committees were established which reviewed all the maternal deaths in their districts and held meetings open to all practitioners to discuss them along much the same lines as those outlined in the Report. Such meetings have constituted a very real addition to postgraduate education in obstetrics and

have been instrumental to a very considerable degree in the gradual reduction in maternal mortality in this country.

Between 1933 and 1940 there was a fall in the maternal death rate from 61.9 to 37.6 per 10,000 live births. Statistical analysis shows that this fall was accounted for by the diminishing number of deaths from accidents of labor, shock, hemorrhage, and the toxemias of pregnancy. This was the result of better obstetrical care due, I believe, to an awakening of the profession to its responsibilities and of the public to the necessity for prenatal care, to the better training of an increasing number of obstetricians and a wider distribution throughout the country of those so trained, to the use of blood transfusion, not as a last resort, but as a preventive of disaster, and to an appreciation of the general surgical principle that in all operative work gentle handling of tissues is a prime necessity. These were in general the desiderata laid down by the Academy Report.

I cannot but believe that the 40 per cent reduction in maternal mortality between 1933 and 1940 was a direct outcome of that Report, together with that of the "Fifteen States Study" and of the Philadelphia group with which the name of Dr. Philip F. Williams will always be associated.

During these years up to 1940 the reduction in the number of deaths from sepsis had not kept pace with that due to the other causes above mentioned. It was about 1940 that the sulfonamides, and shortly thereafter penicillin and other antibiotics became generally available. From then on the death rate from sepsis began to fall even more rapidly than that from other causes, so that in 1950 the total maternal mortality in the United States was only 8.3 per 10,000 live births, truly a striking contrast to the 67.3 twenty years previously.

Obstetricians may take pride in the fact that, led by such men as Dr. George W. Kosmak, they met the first challenge head on and so prepared the way to take advantage of every ancillary aid which modern medical science continues to provide.

## THE AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

### Its Origin, Progress, and Accomplishments

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THE American Board of Obstetrics and Gynecology was organized with the intent of supervising, not controlling, the practice of obstetrics and gynecology by specialists, and will have functioned for a quarter of a century within the next few months. Prior to the formation of the specialty boards, there were numerous self-appointed specialists and the public was accustomed to ask who is a specialist rather than to inquire what a specialist is. There were no criteria whereby either the lay or medical public could distinguish between those who were well qualified and those who were not, and the justification for the establishment of standards to fix the requirements for legitimate specialization appeared to be self-evident.

In September, 1927, I introduced a resolution at the meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in Asheville, North Carolina, providing for the appointment of a committee on standardization of requirements for specialists in obstetrics and gynecology and suggesting the designation of a similar committee by the American Gynecological Society. The primary function of these committees was to consider ways and means for the organization of an American Board of Obstetrics and Gynecology. In May, 1928, the American Gynecological Society appointed its committee and in September of that year the two committees met in Toronto, Canada, and proposed the election of nine members; three by the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, three by the American Gynecological Society, and three by the Section on Obstetrics, Gynecology, and Abdominal Surgery of the American Medical Association. The committee's formal report included a statement of the objectives of the Board, the general requirements for applicants, and a provision for the examination of voluntary candidates and the certification of those found qualified. In July, 1929, I introduced another resolution at the meeting of the Section on Obstetrics, Gynecology, and Abdominal Surgery of the American Medical Association in Portland, Oregon, committing the Section to cooperate in the establishment of the Board, which was unanimously adopted. Shortly thereafter application was made to the State of Delaware for a Certificate of Incorporation which was granted and filed in the Secretary of State's office on Sept. 12, 1930. The three original incorporators were Grace B. Little, Murray R. Spies, and Reed B. Dawson, all of New York. Mr. Dawson has served as the Board's counsel throughout its entire existence.

The Board held its organization meeting and adopted its By-Laws at the General Brock Hotel in Niagara Falls, Canada, on Sept. 14, 1930, with the

following members present: Dr. Walter T. Dannreuther of New York, Dr. Paul Titus of Pittsburgh, and Dr. Grandison D. Royston of St. Louis, who represented the American Association of Obstetricians, Gynecologists and Abdominal Surgeons; Dr. Jennings C. Litzenberg of Minneapolis, Dr. Joseph L. Baer of Chicago, and Dr. Edward A. Schumann of Philadelphia, who represented the American Gynecological Society; and Dr. Fred L. Adair of Chicago, Dr. Robert D. Mussey of Rochester, Minnesota, and Dr. Everett D. Plass of Iowa City, who represented the Section on Obstetrics, Gynecology, and Abdominal Surgery of the American Medical Association, with Mr. Dawson present as legal adviser. At this meeting, the Board voted to invite some two hundred obstetricians and gynecologists who were Fellows of one of the two National societies or held professorial titles in the medical schools to apply for certification without examination. This list was supplemented with additional names until December, 1931, since when all applicants have been subjected to examination regardless of their professional position.

Members of the Board automatically become Directors of the Corporation, each with the same rights, privileges, and responsibilities. The sole reason for electing officers is for the orderly transaction of business. Since the foundation of the Board, all of the original members but one have retired or resigned and have been replaced by others. There have been twelve such changes to date. All Board members have held professorial positions and have served without compensation except for expenses and a modest honorarium paid to the Secretary.

Having been conceived in idealism and born into the world as a result of hard labor, the Board's further activities proceeded from the Articles of Incorporation which state that the chief purposes of the Board are "To encourage the study, improve the practice, and advance the cause of obstetrics and gynecology, subjects which should be inseparably interwoven; and to grant and to issue to physicians, duly licensed by law, certificates or other equivalent recognition of special knowledge of obstetrics and gynecology." The Board promptly instituted a survey of the existing facilities for postgraduate training in obstetrics and gynecology, undertook to persuade hospitals and medical schools to provide adequately for such training, outlined the qualifications that obstetricians and gynecologists should have before announcing themselves as specialists, and endeavored by every means possible to inculcate the idea that obstetrics and gynecology are but two phases of the same specialty and should be combined in a single department. The Board has always required that an applicant be of high ethical and professional standing, that he have not less than three years of formal residency in the specialty after the completion of an internship, at least minimal bilateral training, and a knowledge of the fundamentals of both obstetrics and gynecology. He must also have some experience in private practice, be accepted by his local colleagues as a competent practitioner of the specialty, and assure the Board that he limits his practice and intends to continue to do so.

In some quarters the motives of the Board were viewed with suspicion and considerable skepticism and its personnel was mistaken for a self-appointed



autoeratic group who presumed to dictate to the profession. Sporadic instances of adverse criticism and hostility had to be overcome, and in this campaign four stalwart characters, Dr. George W. Kosmak of New York, Dr. John O. Polak of Brooklyn, Dr. C. Jeff Miller of New Orleans, and Dr. Frank W. Lynch of San Francisco were of tremendous help. Dr. Kosmak's enthusiastic support from the inception of the Board has been invaluable, as he was instrumental in having The C. V. Mosby Company assent to making the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY the official organ of the Board, and has always accepted its publicity for monthly publication in the JOURNAL.

The first written examination was held on March 13, 1931, and the first oral, clinical, and pathological examination was given in the Philadelphia General Hospital on May 6, 1931. There were 79 candidates, of whom 65 were successful, and it is interesting to note that one of the latter group is presently a member of the Board. With the addition of these to the 156 who had already accepted certificates without examination, the Board had 221 diplomates in 1931, contrasted with the 3,908 it has now. In the early days of its operation the Board conducted its examinations in hospitals and utilized patients to test the candidates' clinical ability, but this custom had to be discontinued after the number of candidates became unwieldy. The hospitals were uniformly courteous and cooperative, but it was obvious that the influx of so many people at one time was disrupting their routine work. Until recently the Board has met in various cities, usually at or near the time of the meeting of the American Medical Association, but it has now decided to meet each year in Chicago because that city is easily accessible from all parts of the country and because a permanent set of microscopic slides and gross pathological specimens can more conveniently be maintained in one place.

It certainly is not unduly exacting to expect one who professes to be expert in the diseases of a limited field to be familiar with the intrinsic pathologic alterations in the tissues involved, but there is no doubt that before the Board required a knowledge of the pathology of the common obstetric abnormalities and pelvic diseases and neoplasms many obstetricians and gynecologists were quite indifferent in this respect. As a result of the stressing of pathology in the examinations it is probable that the specialists certified by this Board know as much of this subject pertaining to their specialty as any other clinical group in the country. In the beginning the oral, clinical, and pathological examinations were given by the nine Board members alone. As the number of applicants increased it became apparent that this was an impossible task, so since 1938 an additional group of fifty-three different assistant examiners has been enlisted to participate. In 1953 sixteen additional examiners were needed for the grading of 357 candidates. This practice has served to broaden the Board members' points of view as examiners and familiarized many of the leaders of our specialty with the Board's procedures.

The Board has repeatedly refused to sponsor or lend its support to extraneous activities in the field of obstetrics and gynecology, adhering strictly to the principle that its sole business is to put the stamp of approval on qualified



specialists. It has also often been importuned to waive its requirement for strict limitation of practice, but has firmly contended that expertness in a specialty cannot logically be combined with comparative mediocrity in other branches of medicine. It has consistently refused to lower its requirements for eligibility so that its certificate might be accepted as a reliable criterion for the identification of a capable specialist. Not long ago tremendous pressure was brought to bear to accept as candidates a small number of skillful pelvic surgeons who were concentrating on the super-radical treatment of pelvic malignancies but who were ineligible because they lacked obstetrical training. It seems questionable that a pelvic surgeon, no matter how skillful, who has had no obstetrical experience can have the proper perspective when operating on women in the childbearing period.

Although separate certification in obstetrics and gynecology was debated at length at the organization meeting in 1930 and has been under consideration from time to time since then, after a full discussion it had always been rejected until 1951. The Board then made a concession to those who had been graduated before 1939, who had confined their practice to obstetrics or gynecology for five years immediately prior to application, and who would surrender and relinquish any certificate they might hold from one of the other specialty boards. To date only nine obstetricians and six gynecologists hold unilateral certificates. The members of the Board have unanimously believed that the intelligent practice of gynecology, which is 80 per cent nonoperative, depends in a large part upon a thorough knowledge of obstetrics, and vice versa. The final conclusion after many arguments in each instance has been that indiscriminate unilateral certification would compromise the Board's efforts to encourage the training of all residents in both branches and thus indirectly undermine its other objectives.

The progress made by the Board is exemplified in many ways. Not only has all hostility and antagonism to the Board's purposes disappeared, but some seventy-five professors of obstetrics and gynecology have volunteered their time and efforts to its work. Mushroom specialists are now practically nonexistent. There can be little doubt that the principles on which the Board functions have promoted the unification or at least the correlation of obstetrics and gynecology in a substantial additional number of medical schools and hospitals, and that the cumulative trend toward such amalgamations is still gaining momentum. As a result of this transition, a constantly growing percentage of potential specialists is being exposed to better basic training in both branches. Many pre-existing residencies have been lengthened and new ones created, but despite this amplification of educational facilities, the available residencies, which are approved jointly by the Council on Medical Education and Hospitals of the American Medical Association and the Board's Committee on Graduate Education, are still inadequate in number. In 1931 there were 83 approved residencies in obstetrics and gynecology, including 170 positions; in 1953 there were 414 residencies, including 1,728 positions. The Board therefore is compelled to continue making some provision for preceptorship training and to

accept postgraduate apprenticeship and clinical experience under approved supervision in lieu of part of the required formal training in some instances, much against its inclination.

Aspirants for certification realize that they must prepare themselves thoroughly before presenting themselves, which stimulates them to compile good obstetrical and gynecological records, to read and to study, to attend medical meetings, to take postgraduate courses, and otherwise to augment their qualifications so that they may pass their examinations, habits which are likely to persist throughout their professional lives. The Board also demands that a candidate must acquire sufficient experience in private practice before seeking recognition as a specialist, because unless he practices for a reasonable time on his own responsibility his integrity and ability as a practitioner cannot be determined. In 1931 there were 79 candidates for examination; in 1953 there were 357; and the diplomates to date\* number 3,908.

During World War II the Armed Forces adopted certification by one of the specialty boards as their standard for specialty qualification. It also seems quite natural that medical schools, hospitals, and special societies should evaluate for themselves the significance of certification and utilize it as they choose, but it should be distinctly understood that whatever action has been taken in this respect has been entirely spontaneous and has originated outside the boards. The definite reduction during the past twenty-five years in the previous inexcusably high maternal mortality rate has in all likelihood been due to the fact that hospitals have tended to enforce more obstetrical consultations and to impose restrictions on inexperienced obstetricians.

It would be presumptuous and unwarranted to imply that all of the advances in obstetrical education and practice during the past twenty-five years have been due to the accomplishments of the Board, but that it has exerted a powerful influence for good and has had a salutary effect on the elevation of obstetrics and gynecology as a specialty must be conceded. The members of the Board have tried to exercise their best judgment at all times, regardless of censure or applause.

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\*Exclusive of 1954 diplomates.

## MORTALITY ASSOCIATED WITH MATERNITY

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THE casualties associated with maternity are related to empiric experience and scientific knowledge and the interest in and ability to apply such knowledge. Empiricism may or may not be confirmed by subsequent experience or scientific investigation. Unless there is interest in receiving the benefits of such experience and knowledge and applying them by those who are responsible for their utilization the results are negligible. If they are applied to the few by the few then the results are limited, but if generally used they become of great interest and value.

For progressive improvement, certain ideas must prevail: (1) the empiric and scientific knowledge must be sound, (2) it must be applicable, (3) it must be applied, (4) the agent must be informed and capable, (5) the agencies must be available, (6) the recipients must be willing and cooperative, (7) the testing of existing knowledge and methods must be continuous, (8) the search for new facts must be constant, (9) the substitution of proved new knowledge for older unsubstantiated ideas must be made, (10) the expansion of educational and institutional facilities must be commensurate with the needs.

Maternity presents a unique problem in medical practice because two individuals, mother and fetus, have their health and lives involved at the same time. The saving of one may involve hazards which may result in disability or death for the other. At times this involves critical decisions based upon personal attitudes, professional ethics, legal or ethical or religious concepts. Fortunately, medical progress has made the necessity for such decisions less frequent now than during past decades and centuries.

The scope of this discussion will be limited primarily to the present century and in subject matter it will be general and there will not be elaborate statistical presentations or analyses. Some trends will of necessity be included relative to fetal, neonatal, and maternal mortality. As a background, certain historical references will be made to certain factors which have tended to impede or accelerate progressive improvement.

One factor has been the resistance on the part of some to the acceptance of newer ideas which tended to overthrow prevailing concepts. The experiences of such protagonists as Holmes, Semmelweis, and Pasteur illustrate this point.

The contagiousness of puerperal fever was clearly recognized by Holmes about 1843. His deductions from study of clinical experiences were clear and convincing but met with opposition from clinicians of prominence, who should have been persuaded by his logical reasoning that this disease was conveyed

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to patients by contaminated hands of the attendants. A few years later Semmelweis by carefully made comparative clinical studies should have convinced his colleagues that the disease was carried by unclean hands from the autopsy room and diseased patients to those new patients who subsequently came under care. His ideas were not accepted generally and met with much skepticism even in the higher medical circles. Some 30 years later Pasteur ushered in the bacteriologic era and the scientific basis for the contagion was established. Even then there were many skeptics, and others unfamiliar with this knowledge.

Many of those who were graduated from the medical schools prior to 1890 received inadequate medical education and clinical experience in the schools and under preceptors who were poorly qualified and not abreast of the newer knowledge. Many of these men continued to practice well into the present century. Through the work of Pasteur, Koch, Lister, and others, bacteriology became an established science and a part of clinical medicine and filtered into the medical schools after 1900 often as a stepchild of pathology. There were many low-grade medical schools (diploma mills), but even those who were graduated from the better schools prior to 1890 had little basic knowledge of bacteriology. At that time there were practically no facilities for postgraduate or continuing education. These earlier graduates had little opportunity for subsequent education in the basic sciences or in clinical training.

A technical advance of great importance contributing to clean hands was the introduction of rubber gloves. Their use met with the opposition of some who felt that they interfered with dexterity and the tactile sense. Improvement in the gloves themselves and the gradual extension of their use in hospitals and eventually in home deliveries have contributed greatly to the safety of deliveries.

The important factor was that the infectious theory of diseases involved, in the minds of those educated during the nineteenth century, a fundamental change in their ideas regarding the causation and spread of these contagious diseases. Their practice was naturally influenced dominantly by their education and training. It seems fair to conclude that this present century ushered in a marked change which among other things had a favorable but gradually developing influence on the incidence of puerperal fever.

Statistical reports at the national level, as issued by the National Office of Vital Statistics, of the new Department of Health, Education and Welfare, give much valuable information but the more specific it is the less accurate it is likely to be because detailed and reliable data are dependent upon the completeness and accuracy of the original reports. This material has become progressively more accurate and inclusive as the years have passed since 1900.

It is logical that death reports should be the first to be accumulated at the national level and these are of some value as far back as 1900. The Registration Area was started in 1915 with 10 States and the District of Columbia.

Birth and death reports are not given for the continental United States until 1933. From 1915 to 1932 this area was an expanding one and certain estimates were made to show the national picture. During this time certain procedures have been changed so that the data from year to year had to be



adjusted according to certain set rules regarding live births, stillbirths, deaths, etc., and their causes, thus affecting the relative frequency in certain categories.

Rates are set up for comparison of deaths from various causes based upon population, live births, either estimated or reported, and depending upon the purpose for which the data are used. Rates should not be confused with percentages.

Data relative to stillbirths (fetal deaths) are given beginning in 1942 and now include those of 20 weeks' gestation or more born without sign of life. The incompleteness and inaccuracy of these reports is probably considerable but like other reports they are improving year by year.

The mass data do, however, show certain trends which are important and clearly demonstrate the improvement in obstetric practice as measured by lowered mortality of mothers and infants. Maternal mortality rates in 1915 were about 61 per 10,000 live births. There was a precipitous rise to over 91, during the years of World War I, due to epidemic infections, but the rate was persistently higher, ranging between 62 and 80, until 1934 when it was a little above 59. Since then the decline has been steady until now the rate is below 10 per 10,000 live births.

It seems obvious that something must have happened about 1930 to cause this rapid improvement. A general improvement in health conditions is shown by the progressive reduction in total mortality per 1,000 of population, from 17.2 in 1900, to 13.2 in 1915, to 10.9 in 1932, and less than 10 since 1948.

The infant death rate has shown a progressive downward trend since 1915 but the drop is not as abrupt as that for maternal mortality.

One of the most striking changes since 1930 has been the rapid increase in the number of hospital deliveries. In the early thirties the percentage of deliveries in the hospital was about 35 but at the present time it is over 90 for the nation at large and nearly 100 per cent in many areas, especially the metropolitan.

This has been accompanied by a reduction in the total number of deliveries by midwives who now deliver less than one-third as many as in 1930, with a corresponding increase in the number of deliveries by doctors mostly in hospitals.

It is interesting to note that the fetal death rate (stillbirths) in terms of live births varied only slightly from 1922 to 1930, the low being 38.1 in 1925 and the high 40.2 in 1928. Since 1931 there has been a steady reduction from 38.2 to 22.9 in 1950. This is probably even greater as there is undoubtedly more complete reporting, especially of earlier gestations, with the increased number of hospital deliveries. It would be logical to expect a corresponding reduction in the rates of neonatal deaths, which include those during the first month of life. This rate was 41.5 (1920) per 1,000 live births, the low rate was about 24 in 1932, in 1933 it was approximately 32, in 1940 around 30, and by 1950 it was 20.5. During this period the deaths under one day remained rather constantly at a rate of about 15 from 1915 to about 10 in 1950. There is room for considerable error in evaluating these reports as the statistical practices have changed and are still far from uniform in the various states. There is confusion between live birth and stillbirth or fetal death which was greater in times past than it is today; there are also errors relative to the gestational age and signs of life.

Earlier there was no separate stillbirth certificate but instead there was a birth certificate and an ordinary death certificate to be filled out for each stillbirth. It is therefore difficult to show accurately trends in fetal deaths and

early infant deaths. There does seem to be a definite improvement since the thirties though it is not as marked for the first month of life as for the subsequent eleven months. It hardly needs mentioning that now more of this neonatal period would be spent in the hospitals, especially by the prematures. Their mortality rate is obviously high. Hospitalization does not necessarily mean greater safety but it is a means to that end. There have been some in the past who have argued that it was safer, from the standpoint of infection, to be at home rather than in a hospital. That may have been true in the past but now it would seem to be no longer valid.

Increased hospitalization has undoubtedly been an important factor in the reduction of the mortality of mothers, fetuses, and newborn infants. There has been a fundamental change responsible for the increased hospitalization which is the development of the idea that health is a community responsibility and that mothers and their babies are entitled to better and more complete care. Increased hospitalization required an increase in the number of available beds by remodeling, additions, or new construction, or all of these. This was necessary even though the number of births remained about the same but there was also a marked increase in the total number of births. The estimated number in 1915 was 2,965,000; 2,155,105 were registered in 1935, with a progressive increase to 3,632,000 in 1950. In 1935, 36.9 per cent were delivered in hospitals but in 1949 the percentage was 86.7 which means a numerical increase of 1,404,424 deliveries. More recently some institutions have favored the earlier discharge of patients which would mean that more women could be delivered during a year. There are many factors which have contributed to this increased utilization of hospitals but undoubtedly the chief one is that it is possible to obtain better care for mother and babies, especially premature infants.

The recognition of maternal care as a community problem, instead of solely as an individual relationship between a doctor and a patient, is one of the most important factors in the reduction of maternal and infant mortality during the current century.

Complete and adequate maternal care which is being developed in practically all areas of the United States has ushered in an era of prophylactic obstetrics.

A beginning was made in Boston about 1901 by cooperation between the Instructive Visiting Nurse Association and the Boston Lying-in Hospital in the establishment of home visits on prospective maternity patients.

An early, if not the first, attempt at citywide coverage for maternal care was started in Minneapolis, in 1911. This was a cooperative program involving the Municipal Hospital, The Department of Obstetrics and Gynecology of the University of Minnesota, The Visiting Nurse Association, and the Infant Welfare Society. It included prenatal and postnatal clinics, home and hospital delivery, and puerperal care, with nursing and medical attendants. These clinics were available for the education of medical students and nurses. Home nursing as well as hospital care was available to practitioners for their private cases. At that time hospital facilities were not available for all of these patients but hospital facilities have been gradually increased so that now midwife care and home deliveries have practically disappeared. This program was extended to practically the entire state of Minnesota, as is true of many other states. In 1933 about 43 per cent of all births were in hospitals and in 1950 it was 98.3 per cent. In 1936 doctors attended 96.7 per cent of the births and in 1950 it was 99.8 per cent.

A mortality study made in 1941-1942 showed a maternal mortality rate of 2.0 per 1,000 live births and a similar study in 1950-1951 gave a rate of 0.6.



In other states the situation is more complicated largely due to race and environmental conditions. In Georgia, for example, though the maternal mortality rate has been remarkably reduced, much remains to be done. In 1930 this rate was 109 per 10,000 live births, in 1935 it was 72, and in 1952 it was 13.2, but the rates for white and nonwhite were 5.9 and 25.8, respectively. If this is viewed from another angle, one-third of the live births were in the nonwhite, but 70 per cent of the maternal deaths occurred in the nonwhite group. In 1935 the relative percentage of maternal deaths among whites and nonwhites was 52.8 and 47.2, so it is apparent that there was a greater improvement among the former than the latter. In 1935, 86 per cent of the whites were confined by physicians and 21 per cent of the nonwhites. In 1952 the corresponding percentages were 98.5 and 52.8. Hospital deliveries for the whites were 95.2 per cent and for the nonwhites the percentage was 44.0. All causes of maternal deaths are more prevalent for the nonwhites than for the whites, indicating a lower level of total maternal care for them than for the whites.

Infant mortality is of interest to all but the neonatal mortality is of special importance in connection with maternal and obstetric care. Prematurity remains as the principal problem so far as infant mortality is concerned though per se it should not be considered as the cause of death. In Minnesota in 1950, 35 per cent of the neonatal deaths occurred in the premature group and 65 per cent were in the term infants. The causes of these deaths, as stated on the death certificates, unless confirmed by autopsy, are not very accurate. It is of great importance to determine from clinical history and autopsy the real causes of these deaths. Under a grant from the United States Children's Bureau a study was undertaken at the University of Minnesota, beginning about 1920, to check the causes given on the death certificates with the clinical history and the findings at autopsy. It was not always possible to determine the causes even then but the findings proved that the causes assigned on the death certificates were both incomplete and inaccurate. Later, after 1931, similar studies were begun at the University of Chicago and expanded with the cooperation of the Chicago Board of Health and others. Obviously a knowledge of the causes of death is essential before any preventive or curative measures can be established.

These causes may arise from hereditary, congenital, intranatal, or post-natal conditions. Malformations, birth injury, and anoxia are among the major causes.

Now all infants born with any sign of life must be reported as liveborn even though those of less than 28 weeks' gestation and weighing less than 1,000 grams have little chance of survival. Most of these should be placed in a previable group as they are not equipped for extrauterine life. Those of lesser weight fall into the abortion group which together with those classed as previable make up a large number which may be considered as fetal wastage. The problem of abortion is a complicated one involving medical, legal, social, ethical, and religious viewpoints. Medically, abortions may be divided into intentional and unintentional groups. The former fall into therapeutic and illegal groups. The total number is not known but apparently the number is diminishing. The therapeutic group is surely less in number due to better treatment of the conditions which formerly indicated such a procedure. National statistics indicate that the number of deaths from abortion is being reduced as the rate per 10,000 live births was 6.9 in 1939 and 1.1 in 1949, which is a reduction of 84 per cent. How much of this lessened mortality was due to a decreased incidence of abortions and how much to better management of these complications with decreased number of infections and hemorrhages it is impossible to know, as we have no accurate knowledge of the total num-

ber of abortions. In 1949 of the 3,216 maternal deaths, 394, or 12 per cent, were attributed to abortions and in 1950 of 2,960 maternal deaths, 316, or 10.7 per cent, were assigned to abortions; of the latter, 108, or about one-third, were admittedly induced for legal or unspecified reasons. Sepsis was the assigned cause in 66 per cent in 1949 and 60 per cent in 1950. The Maternal Mortality Study of the Children's Bureau of 1927-1929 comprised 7,380 maternal deaths. Abortion was a factor in about 24.5 per cent of the cases, and infection was the cause in over three-fourths of the cases. It appears that the reduction of maternal deaths from abortion and its complications has been a factor of some importance.

In this study there was a total of 2,948 women who died of puerperal septicemia, of whom 618 were delivered in the hospital and 2,299 were not. Sepsis developed in the hospital in 181 and outside in 1,262.

The rates were definitely higher in the rural areas than in the urban and among the nonwhites than the whites. The technique was more nearly and more frequently but not always more satisfactory in the hospitals than in the homes. Among 4,965 women who were delivered in the last trimester, only 1,740 were known to have had satisfactory aseptic technique. Rubber gloves were used, for vaginal examination and delivery in 3,162 of these women but the prior examination without the use of rubber gloves by midwives or doctors is not excluded. In any case the use of rubber gloves does not, per se, rule out poor technique as they are simply a safeguard if properly used. This study also showed that the rate per 10,000 live births was higher in rural than in urban areas which was particularly true of deaths from infection and during the first two trimesters. There was little difference in the rates of death from toxemias. The rates for the nonwhites were about twice as great as those for the whites, which was particularly true of deliveries in the last trimester.

Our national statistics show the rates for puerperal deaths per 10,000 live births in 1930 were 67.3, for the whites 60.9, for the nonwhites 117.4. By 1949 these rates were reduced to 9.0 for all races, 6.8 for the whites and 23.5 for the nonwhites. For the urban areas of 10,000 or more population the rates were 7.4, for the whites 5.7, for the nonwhites 19.2, the corresponding rates for the rural areas were 11.4, for the whites 8.4, for the nonwhites 28.9.

There may be some racial differences but it appears logical to conclude that environmental conditions played a very considerable role. Among these factors are the increased percentage of care by physicians, from less than 40 per cent in 1935 to about 95 per cent in 1949, the increased percentage of hospital deliveries from 36.9 to 86.7 per cent in the corresponding periods. The percentages for the corresponding periods for the whites were 39.6 per cent and 91.6 per cent and for the nonwhites they were 18.2 per cent and 55.1 per cent. The care by physicians for the same years was for the whites 93.6 per cent and 98.5 per cent and for the nonwhites 44.6 per cent and 71 per cent, respectively. The number of deliveries by midwives diminished proportionately but some midwife cases were eventually delivered by physicians.

In addition to these environmental conditions there are many for which the physicians cannot assume responsibility, such as poverty, ignorance, with the accompanying faulty nutrition, housing, clothing, etc. Some of this can be overcome by better lay education and improved facilities for health to which physicians can contribute as good citizens but governmental and voluntary agencies must assume the major responsibilities.

An important role has been played in the development of better maternal care by voluntary and governmental health and welfare agencies at local, regional, and national levels. Most important have been the activities of the American Medical Association and other professional and lay groups in im-

proving medical education in general and more specifically in the gradual development of better didactic and clinical teaching and experience in obstetrics.

Another vital improvement has been the better hospital standards which have been promoted by the American Medical Association, the American College of Surgeons, the American Hospital Association, and others. This has led not only to better care of the patients but also to improved education and training of the various professional groups, particularly the medical and nursing personnel. The increased number of hospitals with internships and residencies with maternity services and the greater use of these institutions, strategically located for student education and training, have been of tremendous value in furthering the interest in and experience with maternity problems and their solution.

Beginning with this century there seems to have been an increasingly active interest in the care of mothers and their infants. This was not limited to the United States, as Ballantyne wrote prophetically in 1906: "The obstetrician of 1940 will find it difficult to understand why his brethren of the early part of the century paid so much attention to the one month of the puerperal period and so little to the nine months of pregnancy."

The American Association for the Study and Prevention of Infant Mortality (1909-1910), later the American Child Health Association, was liquidated in 1935 after the successful conclusion of the White House Conference on Child Health and Protection which began in 1929. Out of the former came the Joint Maternal Welfare Committee (1919) from which developed the American Committee on Maternal Welfare, Inc., in 1934. The members of this organization have participated in most governmental and voluntary agency activities pertaining to maternal care and have sparked many of them.

Probably the most important factors in the reduction of maternal, fetal, and infant mortality have been the acquisition and dissemination of knowledge and its application among professional and lay groups. That of the professional group might be called the vertical as it involves the few who become the teachers and practitioners of the old and of the new while the dissemination of this knowledge and practice among the masses who profit by its application could be termed the horizontal spread. Both are essential but the vertical must precede the horizontal in time. The professional groups include the practitioners of medicine, both general and special, the nurses (private, hospital, and public health), hospital and public health officials. Social workers and educators are also concerned with some problems related to maternity.

Primarily the educational work had to be done in the various medical schools which developed along with other improvements, much better and stronger departments of obstetrics and gynecology. Facilities for clinical teaching had to be developed and integrated with the didactic. This involved the development and utilization of outpatient and hospital clinics. Various professional associations and lay organizations had much to do with the improvement of medical education for students, interns, and residents. The licensure boards of various states were improved and more efficient laws were passed to control the licensing of practitioners of medicine. The National Board of Medical Examiners became of great influence.

Specialization has increased markedly and the American Board of Obstetrics and Gynecology (1930) has had much to do with the elimination of untrained and unqualified specialists and the raising of the standards of practice.

The adequate education and training of these specialists has been made possible by expanded facilities for education and training of undergraduate students, interns, residents, and postgraduate and graduate students, and practitioners.



Along with this there has been a tremendous increase in the number of special obstetrical and gynecological societies and their membership, at local, state, regional, and national levels.

The American Congresses of Obstetrics and Gynecology, of which there have been five in the past fourteen years, have brought together specialists, general practitioners, nurses, hospital and public health personnel, and educators to present and to discuss matters of both special and general interest. All of these activities have stimulated greater interest in the acquisition of knowledge both old and new and the search for further knowledge and better means of its application.

The acceptance of the ideas of prevention and their application has been most important and has been made possible by preconceptional and prenatal care. Preparation for the anticipated pregnancy and expected delivery is most important and means not only proper care but also the earlier detection and treatment of threatening conditions and complications. Personal hygiene, the control of venereal diseases, proper nutrition, the detection and alleviation of toxemias have all been important. Convulsive attacks have been largely eliminated where prenatal care is well established. Proper nutrition is now recognized as most essential in the prevention and correction of certain disorders which complicate pregnancy. These are a few examples of the value of such care.

So far as drugs are concerned notable advances have been made in chemo- and biotic therapy and their influence upon the course of infections is great but they should not lead us to slight or ignore the preventive measures which accomplished so much in reducing mortality before their advent.

The use of blood is now so commonplace that it is difficult to realize the present safety and availability compared with the situation a few decades ago. Blood banks are most essential and their establishment requires foresight. Obstetric hemorrhages are often not only sudden but profuse and may be rapidly fatal unless blood of the proper type and in sufficient quantity is promptly available.

These efforts require cooperation, as do many others, such as mortality studies. Such a one was the three-year study of maternal mortality in New York City published in 1930 by the New York Academy of Medicine. This work had a definite effect in reducing maternal mortality by pointing out the preventability of many such deaths.

Many of the leaders in education who have been interested in securing better maternal care, with a resultant reduction of maternal, fetal, and neonatal deaths, have been instrumental in developing such studies by means of state and local committees. Such committees are cooperative in their work as medical practitioners, both general and special, health agencies, hospitals, and other interested agencies must work together. Death certificates with clinical data and autopsy reports and all pertinent data available are studied to determine as accurately as possible the factors causing the deaths of mothers, fetuses, and infants in the neonatal period. These studies are primarily educational and prophylactic as they seek to remedy the conditions which brought about the casualty. This may be due to the patient's negligence, to professional mismanagement, to lack of proper facilities, or may have been unavoidable. Such appraisals have been very important in the reduction of mortality by correcting errors or deficiencies.

The purpose of this paper has been to present a discussion of the factors which have contributed to the remarkable reduction which has occurred in the mortality associated with maternity. The spotty character of results at the



present time indicates that further reductions are possible in certain geographic as well as in some medical areas. Perhaps the optimal or near it has been attained in certain favored places but there are many much less favored areas.

There is no other field of medicine in which the lives of two or more individuals are so intimately associated and so dependent upon the type of care which is received. The loss of any one of the individuals should be regarded as a failure but, with our present knowledge, not all can be saved from disability or death. There are still many areas in which our knowledge is incomplete and there are still many segments of our population which do not receive the full benefit of the application of our present knowledge.

The reduction of mortality suggests that morbidity has also been cut but specific data about this are not available and were not within the scope of this paper. In some instances disability may result for mother or infant in cases in which, without improved care, death would have resulted.

During the past 50 years statistical data have undergone marked changes both as to their form and completeness, as well as accuracy. This applies particularly to birth and death certificates of mothers, fetuses, and early or neonatal infants.

I have made no attempt to support statements with elaborate statistical tables or graphs. Some statistical data have been given from various sources which seem to support the evidence relative to certain factors. It would not have been feasible to give all the factors and some have been omitted either intentionally or otherwise. There could be much personal difference as to the various factors and as to the influence of certain agencies or activities. It would have been difficult even to enumerate all of the activities of governmental and voluntary agencies to say nothing of evaluating their influence. It has been possible to give a picture of the factors with which my personal experience is most familiar.

In conclusion it could be stated that in times past some taboos about certain conditions and diseases have seemed to check progress in prevention. This has been particularly true of reproductive processes about which the educational sources were far from ideal. Much change has taken place in this regard. It is probable that the widespread showing of "The Birth of a Baby" as an educational film had something to do with improved maternity care.

Just how far sex education should go and how it should be handled, I am not prepared to discuss, nor is it germane to this paper, but a sensible and appropriate knowledge of the processes of human reproduction should be acquired at the appropriate time in a proper atmosphere.

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## CRITICAL EVALUATION OF THE MINNESOTA MATERNAL MORTALITY STUDY

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DETAILED studies of all maternal deaths in the state of Minnesota have been carried out in 1941-1942 and continuously since 1950. All women who died of whatever cause while pregnant or in the following three months are included in these studies. Since 1950, deaths from chorionepithelioma are included in the year in which death occurred. All of these are included as maternal deaths in the Maternal Mortality Committee's calculation of the maternal mortality rate. The results of these have been published,<sup>1, 2, 3</sup> and another report is in preparation. Cases are found through death certificates, reports from hospitals and physicians, from a variety of other occasional sources, and by cross-matching all death certificates of women aged 15 to 45 years with birth certificates. It is probable that almost all maternal deaths are presently found. One of a group of three well-trained obstetricians who hold clinical appointments at the University of Minnesota Medical School goes as soon as possible to the site of the death and collects all pertinent data from the physician, hospital, and pathologist concerned and, when necessary, from the patient's relatives and from other physicians or hospitals. These data are formally put together, summarized, and critically evaluated for the determination of, among other things, accuracy, completeness, reality of cause of death, responsibility for death, and preventability. All of this is carefully checked by others in the Department of Obstetrics and Gynecology and is then presented to a common meeting of the members of a Maternal Mortality Committee of the Maternal Welfare Committee of the Minnesota State Medical Society. This Maternal Mortality Committee makes final decisions on policy and on such matters as cause of death, responsibility for death, and preventability. A detailed report is published once a year under the authorship of the Committee. The three investigators are paid a sufficient amount approximately to defray their expenses. This money has been made available from funds from the Children's Bureau of the Federal Government through the Minnesota State Department of Health. It has amounted to approximately \$3,000 to \$4,000 a year. All other personnel serve without remuneration.

It is perhaps an understatement to say that this study has been of considerable and continuing value. This has been considered in the previous publications.<sup>1, 2, 3</sup> The purpose of the present discussion is to present some of the more general problems which have been faced, the conclusions which may be drawn from an experience of this kind, and to try to justify some conclusions and warn-

ings which the study has forced into attention. It should be clearly stated that the conclusions which follow are those of the present authors and not necessarily those of the Committee as a whole.

### **The Reality of Maternal Mortality Rates**

A study such as is being carried out in Minnesota rapidly teaches a healthy skepticism as to the conclusions which are all too often drawn from maternal mortality rates as they are ordinarily collected and reported. Physicians as a group are notoriously careless of biometric principles while biometricians seem to lose sight of the fact that their careful mathematical handling of data does not justify conclusions unless the raw data themselves are accurate and complete. Let us look for a moment at the source of the maternal mortality data.

An obstetric patient gets into difficulty and more or less accurate study is carried out. A diagnosis of more or less accuracy is made and indeed on occasion an accurate diagnosis may not be possible. She dies and the physician with his pride and prejudice is forced to put the whole sad story into a half dozen words on the death certificate in the space reserved for diagnosis. He should remember to state that the patient has been pregnant at some time within the previous year\* although he does not always do this, and on occasion there may be reasons why he might wish to avoid reporting it. If the death certificate shows that there has been such a pregnancy, this death certificate is now processed by someone with more or less skill and gumption who decides on the basis of an oversimplified set of rules in the International List of Causes of Death and with only the half dozen words written by the doctor, whether this was a so-called obstetrical or nonobstetrical death. If he decides that it is nonobstetrical, it is not included as a maternal mortality. On the basis of data so obtained, it is customary to compare the "maternal mortality rates" of various states where differences in percentage are in the second and third decimal places. And, finally, no consideration is given to deaths which occur more than a year after completion of the pregnancy, no matter how directly the pregnancy may have influenced the end result.

This may seem at first glance to be an exaggerated statement of the possible fallacies involved. In the light of the Minnesota experiences, let us examine each of these steps.

### **Accuracy of Death Certificate Diagnosis**

The investigator and the Committee tried very hard to be fair and accurate. They spent much more time and were much more conscientious than the original physician in arriving at a conclusion. They were free of the original physician's prejudice. Where a diagnosis was not possible because of deficient data, the death was recorded as due to unknown causes.

A number of surprising things were uncovered. There was often a positive diagnosis on the death certificate when none was possible. There were 6 deaths

\*This is the rule applied by the department of vital statistics in Minnesota following the regulations of the National Office of Vital Statistics as published in the Causes of Death Coding, 1952. The Minnesota Maternal Mortality Committee used three months post partum as their definition. There is no time stated on the Minnesota death certificate. There seems to be a real element of confusion here.

(10.3 per cent) in 1951, in which the cause of death could not be determined on careful examination of the details and in spite of the fact that in three cases there were adequate autopsies. A specific but unjustified cause of death was given on the death certificate in all 6. A pregnant woman was apparently well when she went to bed but was found dead in the morning on a balcony off the bedroom. The physician refused to sign a death certificate without an autopsy which was not forthcoming. The coroner, a layman, signed it as due to diabetes which she did not have "to save the family from embarrassment." In circumstances where no diagnosis was possible, a physician supplied one from a fertile imagination because "if I don't, the death certificate will be returned to me and I don't want to be bothered." An occasional diagnosis is falsified because "the less the family know about it, the better." Pulmonary embolism is blamed for all manner of things with which it has nothing whatever to do. One patient whose death certificate showed the cause of death as pulmonary embolus actually died of air embolism from air pumped into her veins under pressure through an empty transfusion bottle. A patient whose death certificate showed epilepsy as the cause of death died of postpartum hemorrhage.

This has quite effectively hidden a great many significant factors in maternal deaths. Perhaps the best example of this is the significance of the injudicious use of spinal anesthesia which is seldom given as a cause of death. The problem of the risk of obstetric anesthesia becomes very clear from a detailed study such as this. Over the same time period in Minnesota there were 10 deaths from obstetric anesthesia and 13 deaths from eclampsia. There seems to be a lesson here for the teacher and the author of texts.

Careful examination of the data obtained has led the Committee to change the death certificate diagnosis in 27.2 per cent of the cases in 1950 and 1951. Even this does not represent the full measure of the error since the diagnoses were more often wrong in the so-called obstetric deaths than in the so-called nonobstetric ones which were excluded from the usual maternal mortality reports. The group classifications of maternal deaths under shock, hemorrhage, infection, etc., and particularly the subgroup headings derived from unchecked data are not accurate as they are usually presented.

### **Completeness of Reporting of Maternal Deaths**

It is hard to know what proportion of maternal deaths escapes recognition as such. Unless the diagnosis makes it obvious that there has been an obstetric association, the usual collection of data is dependent upon the fact that the physician remembers or wishes to remember to record this fact on the death certificate. By the methods previously described, the present study turned up 32 maternal deaths which would not otherwise have been found as against 93 maternal deaths reported in the usual manner. A considerable number of the unreported deaths were so-called nonobstetric deaths but many were not. How easy it is to neglect reporting obstetric association with the death may be illustrated by the fact that this happened to two large institutions represented by members of the Maternal Mortality Committee as well as to several coroners. There is the possibility of a large source of error here. The degree of error in



Minnesota under circumstances of the present study is probably a minimum for obvious reasons.

If one combines the totals of death certificates of maternal deaths which did not list a recent obstetric event and those which carried an incorrect diagnosis of cause of death in 1951, it was found that there were 19 such cases in a total of 57 maternal deaths, or an error of 33 per cent. Since in 11 cases a recent obstetric event was not reported, it might be said that the combined error of missed cases and incorrect diagnosis was 19 of 46, or 41.3 per cent. Under any circumstances the error is large.

A considerable proportion of these deaths which are not recorded as maternal mortalities (Table I) will be picked up by routinely cross-matching reported deaths in women between the ages of 15 and 45 with birth certificates of the previous year. This leaves the abortion group in which a birth certificate is not required (in Minnesota, less than 20 weeks of gestation) unchecked but it will help. One would like to be able to be sure of finding all of these abortion deaths, again for obvious reasons, but there seems to be no way of doing it short of investigating all female deaths in this age group.

TABLE I. SOURCES OF CASE REPORTING IN 1950 AND 1951

	NO.	%	NO.	%
Total maternal deaths (1950 and 1951)			125*	100
Cases found from death certificates (with or without preliminary report from physician, hospital, etc.)			93	74.4
Sources other than death certificates			32	25.6
Cross-match of death with birth certificates	17	13.6		
Others	15	12.0		

\*The total of 125 maternal mortalities includes four which were the result of chorion-epithelioma. These are included with the cases found from death certificates.

### Exclusion of So-called Nonobstetric Deaths

It is not easy to understand how this concept ever came to be accepted. The physician will probably never be very smart in the handling of the mathematical problems of the use of statistical material but he may reasonably be expected to think his way through the reality of the accuracy of his basic data, the problems of automatic or artificial selection of his material, the foolishness of excluding findings without first reporting them as a gross figure, and the risks inherent in the use of small numbers. The biometrician might reasonably be expected to acquaint himself with the accuracy of and the methods of obtaining the data with which he works before putting the seal of mystic mathematical infallibility on his conclusions. There is no end to the examples which could be cited.

In addition to the inaccuracies of the basic data from which conclusions are reached as to the details of maternal mortalities, we now in our great wisdom add an artificial selection and an unreported exclusion. It must be pointed out again that this is done on the basis of a half dozen words on a death certificate, written by one who is often enough a careless or a prejudiced observer and interpreted by a person who may be uninterested and untrained. Not only are the data often insufficient to allow such a decision as to obstetric or nonobstetric causes but basic principles which are applied are not acceptable.

TABLE II. PERCENTAGE OF INACCURACIES OF BASIC DATA

	NO.	%	NO.	%
Total maternal deaths (1950, 1951)			125	100
Death certificate correct and complete in all details	33	26.4		
Death certificate correct in all details reported	<u>37</u>	<u>29.6</u>		
Death certificates incorrect			70	56
Death certificate incorrect as to cause of death			55	44
			34	27.2

An example of the first of these may be taken from the present study. A pregnant woman was in an automobile accident and was admitted to a hospital where, after some 12 hours, she died of shock. This is a nonobstetric death. Actually, the physician missed a readily diagnosable rupture of the uterus which might well have been treated. Autopsy later confirmed this. Do we exclude traumatic rupture of the pregnant uterus from the list of obstetric lesions? Two pregnant patients developed a psychosis, were hospitalized and discharged with a known and admitted risk of self-destruction. Both committed suicide, one by drowning and one by throwing herself under a train. Both deaths could have been prevented. These are also nonobstetric deaths. Was the psychosis not an obstetric problem and was the obstetrician not responsible for protecting the patient and the baby from the known inherent risks? An eighteen-year-old girl who was fourteen weeks pregnant presented typical gastric complaints to her obstetrician. The diagnosis was missed until late in pregnancy by which time the tumor was extensive. A living baby was obtained but the patient died during the course of an attempt at superradical surgery. Earlier diagnosis might have changed this course of events in some degree at least. This would be listed as a nonobstetric death. How far this sort of arbitrary foolishness can go is perhaps illustrated by the fact that one European country with a low maternal mortality was found to exclude eclampsia and to list it under other than maternal causes of death. One could go on and on with such examples from the present study.

It is a basic principle in the use of statistical reporting that all the material involved in the study be reported as a gross figure. Following this, for one expressed reason or another, separate groups may be examined. In the absence of a detailed study of each maternal death, there is no real basis for separation into obstetric and nonobstetric deaths. Even the principles of such separation after complete data are obtained are open to serious question. The possibilities for nature faking here are great and misleading conclusions of importance can result. A move in the direction of reality can be made by reporting as maternal deaths all deaths from whatever cause during pregnancy or in some arbitrarily determined period of time after the completion of the pregnancy.

The end result of all of this is that two figures are now being reported for Minnesota. These are shown in Table III. One of these is the usual figure in the second to last column of Table III and calculated on the basis described, but, it should be noted, this includes cases which were not reported, which were found by the study, and were classified as so-called obstetric deaths. The other

is the uncorrected total of maternal deaths as defined in the preceding paragraph and is derived from the study. They cover slightly different calendar months. The listing of the causes of death as they have been published from the study<sup>1, 2, 3</sup> are as accurate as it is possible to make them and have a quite different basis from similar ones from other places which are derived from death certificate diagnoses alone.

TABLE III. COMPARISON OF MATERNAL MORTALITY RATES FROM THE STUDY WITH THOSE USUALLY REPORTED

	NUMBER DEATHS	NUMBER BIRTHS	GROSS MORTALITY RATE PER 1,000 LIVE BIRTHS*	MINN. MATERNAL MORTALITY RATE PER 1,000 LIVE BIRTHS†	U.S. MATERNAL MORTALITY RATE PER 1,000 LIVE BIRTHS‡
1941-1942	112	55,293	2.03	1.8‡	2.80‡
1950	68	76,074	0.89	0.6	0.83§
1951	57	80,099	0.71	0.3	0.71§

\*Including all maternal deaths from whatever cause. These are the Maternal Mortality Committee's gross figures.

†Excluding deaths considered as nonobstetrical on the basis of the definitions set down by the United States Bureau of the Census. This is the ordinarily reported maternal mortality rate as given by the Minnesota Department of Health.

‡Average for 1941 and 1942.

§Unofficial.

### Some Other Problems of a Maternal Mortality Study

A number of problems will inevitably come for decision in such studies and a few of these will be considered. There are no accepted rules and those responsible for the study will simply have to apply their best judgment.

The most difficult decisions involve the determination of cause of death, preventability, and responsibility for death. In general, it is unwise to quibble with these. If a clear decision can be made, all well and good, but if not it is best to list the cause of death as unknown and the death not preventable. Occasionally, a patient will have died under circumstances which strongly suggest a treatable lesion which, with adequate opportunity, the physician has made no reasonable attempt to diagnose or treat. Under these circumstances, there may be reason to list the death as physician responsibility and then necessarily as preventable. In the determination of preventability and physician responsibility, the Committee is more strict when the physician is or claims to be a trained obstetrician and when the events took place in a large, well-equipped hospital. Considerable leeway is allowed for the physician's judgment when he has made reasonable efforts to collect diagnostic data and used reasonable care in implementing his decision.

Occasionally it is impossible in the absence of an autopsy examination to prove that a patient was in early pregnancy or not. In general, these cases have been excluded.

What should be done with chorionepitheliomas of placental origin? These are not customarily included unless the patient dies within three months or one year of the treatment of the known pregnancy or mole and often are not included at all. There is no death more directly related to pregnancy than that caused by a nonteratomatous chorionepithelioma. In the present study, these have been

included as maternal deaths in the year in which the death occurred rather than in the year of assumed origin.

Should the Committee bring its report to the attention of the physician concerned? In the earlier stages, the report was offered to the physician, but the requests for this information were almost entirely in cases in which the physician was not at fault. This led to some soul searching. A physician operated upon a patient with the mistaken diagnosis of appendicitis only to find a tubal ectopic pregnancy which he adequately handled. She developed some abdominal distention for which nasal suction was applied and left in position for 13 days. During this time she received a little more than a liter of intravenous fluid, a part of which was normal saline. She died with carpopedal spasm. The investigator reported that the physician did not know what he had done. The same situation applied to a hopelessly treated case of pernicious vomiting and to several patients with gross overdosage with spinal anesthetics. A copy of the detailed final report is now sent to each responsible physician with the hope that it will be useful to him. The report is so detailed that it leaves nothing to the imagination.

Far and away the most important part of any such study is the interest and care which the investigator gives to each case. He must be completely detached from any personal interest or prejudice in the case and beyond any possibility of being involved in local pressures of one sort or another. It is obvious that he must be of superior competence in his field. He is asked not to answer technical questions and not to be critical by word or look. It seems clear that the study can be done effectively only from one central interested source. The use of local physicians as regional investigators in their own geographic areas is almost certainly unwise.

### **The Limitations and Values of a Detailed Maternal Mortality Study**

Such a detailed study is valuable in a variety of ways. In the broadest sense it produces information which is a reasonable expression of the efficiency of obstetric care within the area concerned. As has been pointed out previously, it is dangerous to use such data to compare one state with another since the methods of the compilation of data may well be dissimilar.

Unfortunately, it gives no answer to a group of questions of importance. The effect of obstetric procedures and decisions on the fetus in a broad geographic area such as a state is not known. Such information is extremely hard to get. Autopsies on newborn babies are, in general, not carefully done and, even when they are, the relation of the findings to the clinical problems is not easy to draw. It is probable that accurate information about the baby will have to be obtained by sampling techniques.

Maternal morbidity and damage below the level of destruction are clouded by a similar lack of information. But in this field the most important feature is the time limitation of three months or one year post partum which is variously applied to the definition of a maternal mortality. That this is of extreme significance can be illustrated by one example. If one will extend his concept



of the term maternal mortality to include the ten years after delivery, it can be shown that arteriolosclerotic toxemia of pregnancy alone is responsible for at least as many maternal deaths as all other immediate causes combined. The obstetrician must lose his complacent satisfaction in the discharge from the hospital of a patient who survives for three months or one year. He has decisions to make which affect the patient's remote future which, expressed as numbers of deaths alone, are as important as all of those in the year of pregnancy, delivery, and three months or one year post partum.

Another limiting feature of the interpretation of data obtained in a detailed study is inherent in the fact that the patients who die represent an automatically selected sample of the general obstetric material of an area and are unlikely to be a fair sample. Indeed, this sample is likely to be loaded with patients who have had the poorest obstetric care. What is the significance, for example, of the fact that in those patients who died in the three years of the study, only 21.5 per cent had had adequate pelvic mensuration? The same general lack of adequate care is seen in the disappointingly small numbers who had adequate general physical examination, Wassermann and Rh testing, reasonable basic examination on hospitalization, and minimal study of the abnormalities which may have led to death. It is an earnest hope that this sort of negligence or ignorance is not representative of routine obstetric care in Minnesota, but this is only a hope. The council of the Minnesota State Medical Society has refused a request for permission to sample a variety of hospitals. They will be asked again when it is hoped that a more mature judgment will prevail.

On the other hand, real advantages have accrued from the detailed study. It has been a wonderful clinic for those who have taken part in it, so that the interest of the investigators and the members of the Committee has been held at a high pitch. It has supplied information which has changed the emphasis of both undergraduate and postgraduate teaching. Individual physicians have had honest errors pointed up and there is every reason to believe that these will not be repeated by the person concerned. The hopeless inefficiency of the present coroner system in Minnesota is no longer a matter of conjecture.

Odd and surprising situations were brought to light. For example, one community was found to be contributing a large proportion of the placenta previa deaths. On putting these together, it was evident at once that someone in that area had established the concept that accouchement forcé was standard treatment for placenta previa. With this corrected, there has not been a placenta previa death in this area during the past two years.

Such problems are constantly turning up and, once recognized, they can be quietly and effectively handled. Accouchement forcé is responsible for a surprising proportion of the hemorrhagic shock deaths (6 of 13 hemorrhagic deaths in 1951) and a campaign is presently under way to destroy this elderly beast. Obstetricians in general are not effectively using modern knowledge about electrolytes and water. The problem is not any more the lack of availability of blood but the necessity for speed and larger quantity in its use. Of more importance than any other single feature is the fact that, in an astonishingly

large number of hospitals, there is no insistence on routine laboratory study, physical examination, pelvic mensuration, clinical work-up of abnormalities, and such simple things. Here is a hard nut to crack with the prospect, in terms of reduction of maternal mortality, of a really meaty reward. A large proportion of these maternal deaths start off with the lack of recognition of a simple thing such as anemia, a cardiac lesion, or a contracted pelvis, and then build themselves up into a complicated irreversible situation. It is not unusual that a death certificate lists hemorrhage or infection when the patient actually died because accurate pelvimetry was not done at the first prenatal visit.

One could go on more or less indefinitely with such listing of the advantages of a detailed and continuing maternal mortality study. Enough has been discussed to make it clear that the conclusions to be drawn from such a study must be approached with caution. On the other hand, much information which is of real practical value can be obtained by this method of approach which will not be evident from the usual methods of case finding and reporting. Judicious application of this information can lead to improved efficiency of obstetric care and increased safety for mothers. It is difficult to imagine a more useful and satisfying practical medical enterprise and for these reasons it is recommended for general application.

### Conclusions

1. The more general problems and experiences of a detailed continuing maternal mortality study in the state of Minnesota are discussed.
2. In the absence of a detailed study, maternal mortality data as they are usually collected and reported are not reliable since the material on which they are based is grossly inaccurate.
3. Maternal mortality rates are not a real expression of what might be called obstetric risk since they exclude so-called nonobstetric deaths and do not measure morbidity and damage, fetal damage and destruction, and late maternal damage or destruction.
4. A plea is made for discontinuing the arbitrary exclusion of so-called non-obstetric deaths from gross maternal mortality reports.
5. Routine cross-matching of death certificates of women between the ages of 15 and 45 years with birth certificates can be done readily and will increase the efficiency of case finding.
6. An accurate statewide maternal mortality study can be carried out at small cost. It will yield information of real practical importance. Examples are discussed.

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## PROBLEMS OF MATERNAL MORTALITY IN JAPAN

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**D**EATHS of women during pregnancy, which form approximately one-third of all maternal deaths in Japan, result in the loss of fetuses as well as mothers. Deaths of women after delivery may be responsible for the increase in the infant death rates because of the unavoidable deficiencies in the post-natal care. Maternal deaths may be associated with abortions, premature labors, or stillbirths. Thus maternal mortality plays an important role in population statistics.

The yearly change in mortality rates in Japan during the past five decades, together with some detailed statistical data collected during the last few years, to be presented here, have been worked out by the Maternal and Child's Health Section, Children's Bureau, Ministry of Health and Welfare, on the basis of the International Lists of Statistical Classification of Diseases, Injuries, and Causes of Death.

### Results of Statistics

#### *I. Yearly Changes in Maternal Mortality Rates From 1900 to 1952.—*

The maternal mortality rate around 1900 used to be approximately 40 per 10,000 total births (live births plus stillbirths), but it has gradually decreased until it reached as low as 15.5 in 1952, or to about two-fifths of what it was fifty-two years ago (Fig. 1). Such a downward trend in the maternal mortality rate in Japan during the past five decades suggests an improvement attributable to medical progress in general, but particularly to the expansion of the general ideas of maternal welfare.

It should be remembered, however, that in the United States there has been a "dramatic" reduction in maternal mortality rates during the past three decades from a plateau above 60 to a level of approximately one-fifth that rate in 1948. In 1915 there were 61 deaths, in 1918 as many as 92 deaths per 10,000 live births, or 1.7 times the figures for Japan in the corresponding years. The rate in the United States in 1948 was only 12 deaths per 10,000 live births, a rate low even when compared with 16.8 deaths, the maternal mortality rate for Japan in the corresponding year.

From 1948 to the present time, the maternal mortality rates in Japan have remained more or less stationary at the level of 15 without demonstrating any tendency to decrease. This state of affairs may, to a certain extent, be attributable to undesirable effects resulting from interruptions of pregnancy, which have remarkably increased in number with the liberalization of

indications since the end of the war. An optimistic view toward maternal mortality in Japan in the last few years, however, is not permissible, and some measures should be taken to meet the situation.

As is widely known, childbirth is subject to complications which occur unexpectedly and require prompt attention. Hospitalization is, therefore, essential for bringing about the reduction of the maternal deaths directly connected with the childbirth. In Japan, however, most of the deliveries are carried out at home (95.5 per cent to 91.0 per cent), particularly in rural areas, attended mostly by midwives alone. The deliveries in hospitals are very few in number, as is shown for the years from 1947 to 1949 in Fig. 2.

### YEARLY VARIATION IN THE MATERNAL MORTALITY RATES 1900 to 1952

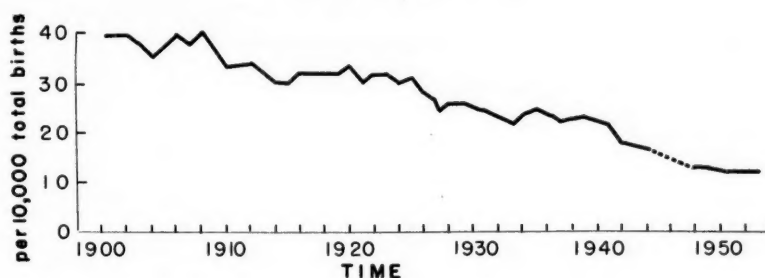


Fig. 1.

### RATIO OF CHILDBIRTH IN HOSPITALS AND IN HOMES

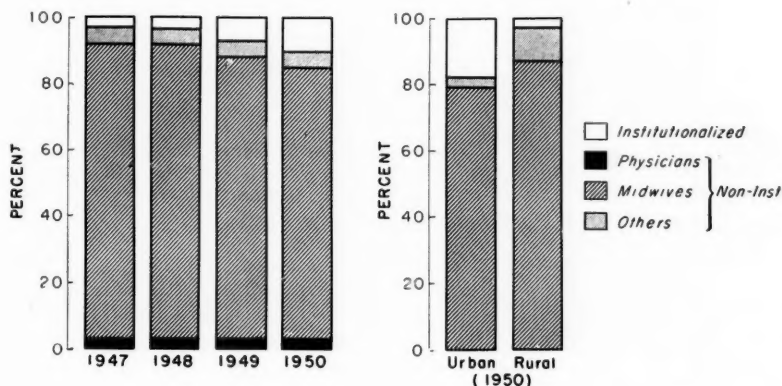


Fig. 2.

I am sure the reduction in the maternal mortality rates in Japan would become more noticeable if the number of births taking place in the hospital could be increased.

#### II. Causes of Maternal Mortality.—

Diseases causing maternal deaths may be divided into two main groups—diseases directly connected with pregnancy, childbirth, and the puerperium



TABLE I. YEARLY VARIATION IN MATERNAL DEATHS BY CAUSE FROM 1947 TO 1949

CODE NUMBER	CAUSES OF DEATH	YEAR		
		1947	1948	1949
XI				
140-150	Diseases of pregnancy, childbirth and the puerperium	4,488	4,437	4,601
140	Abortion with mention of infection (gestation of 7 months or less)	135	128	174
a	With mention of pyelitis	16	5	9
b	With mention of other infection	99	102	145
c	Self-induced	4	0	2
d	Induced by persons other than the woman herself	2	1	9
e	Others	14	20	9
141	Abortion without mention of infection (gestation of 7 months or less)	291	272	278
a	With mention of hemorrhage, trauma or shock, and toxemia	26	10	4
b	With mention of hemorrhage, trauma or shock (but not toxemia)	40	48	44
c	With mention of toxemia (but not hemorrhage, trauma, or shock)	23	14	9
d	Without mention of hemorrhage, trauma or shock, or toxemia	170	179	179
e	Self-induced	11	3	12
f	Induced by persons other than the woman herself	3	0	23
g	Others	18	18	7
142	Ectopic gestation	326	347	336
a	With mention of infection	14	16	26
b	Without mention of infection	312	331	340
143	Hemorrhage of pregnancy (death before delivery)	368	297	224
a	Placenta previa	136	111	89
b	Premature separation of placenta	172	160	124
c	Others	60	26	11
144	Toxemias of pregnancy (death before delivery)	1,138	1,357	1,347
a	Eclampsia of pregnancy	649	740	672
b	Albuminuria and nephritis of pregnancy	369	497	533
c	Acute yellow atrophy of liver (during pregnancy)	14	11	15
d	Hyperemesis	59	47	57
e	Other toxemias of pregnancy	47	62	70
145	Other diseases and accidents of pregnancy (death before delivery)	126	179	169
146	Hemorrhage of childbirth and the puerperium (gestation of 8 months or over, or unspecified)	761	777	903
a	Placenta previa (with childbirth)	76	76	119
b	Premature separation of placenta (with childbirth)	167	198	224
c	Atonic bleeding	251	249	321
d	Other hemorrhage during childbirth	90	55	48
e	Other hemorrhage after childbirth	177	199	191
147	Infection during childbirth and the puerperium (gestation of 8 months or over, or unspecified)	621	488	395
a	Puerperal pyelitis and pyelonephritis	76	36	21
b	General or local puerperal infection (except pyelitis)	524	438	369
c	Puerperal thrombophlebitis	7	7	0
d	Puerperal embolism and sudden death	14	7	5
148	Toxemias during childbirth and puerperium (excluding death before delivery)	120	93	209
a	Eclampsia with childbirth	31	34	67
b	Puerperal eclampsia	46	45	100
c	Puerperal albuminuria and nephritis	17	12	35
d	Acute yellow atrophy of the liver (puerperal)	5	0	4
e	Other toxemias	21	2	3

TABLE I—CONT'D

149 Other accidents and specified conditions of childbirth	445	358	322
a Laceration, rupture, or other trauma of pelvic organs and tissue (except rupture of uterus)	11	7	7
b Rupture of uterus	191	125	105
c Other specified conditions of childbirth	243	226	210
150 Other and unspecified conditions of childbirth and the puerperium	157	141	214
a Infection of breast during lactation	3	0	0
b Psychosis of the puerperium	5	4	6
c Other and unspecified conditions of childbirth and the puerperium	149	137	208
Live births	2,678,792	2,681,624	2,696,638

and general diseases with no direct connection with pregnancy. As is generally known, only the diseases belonging to the former are being adopted in the International Statistical Classification. The statistical data concerning maternal mortality in Japan which will be introduced here are based on the International Statistical Classification with some specific modifications within the authorized limit.

*A. The fifth revision of the International List modified and adopted by Japan:*

In order to demonstrate a modified form of the International List adopted by Japan, its fifth (1947-1949) revision is shown in Table I, in which different causes of maternal deaths during 1947, 1948, and 1949 are compared with each other.

The adoption of the fifth revision in Japan was postponed until 1947 owing to the war. It should be noted that the modifications specifically provided for in the fifth revision by Japan are that hyperemesis, atonic bleeding, and rupture of the uterus were added to the causes of maternal deaths under the code numbers 144, 146, and 149, respectively.

*B. Yearly variations in maternal mortality rates by causes from 1933 to 1951:*

The frequency of the various causes of maternal mortality are listed by years in Table II.

It is to be noted that the figures for 1944, 1945, and 1946 are not available because of the confusions attendant upon the war's end, and that those for the years prior to 1943 include the figures for Okinawa Prefecture.

The mortality rates from 1933 to 1943 were coded on the basis of the fourth revision of the International List. For those from 1947 to 1949 certain adjustments have been made to allow for the changes in coding which went into effect in 1947 with the start of the fifth revision. Thus the code numbers from the fifth revision (1947-1949) 141, 142, 143, etc., for instance, correspond with the code numbers from the fourth revision (1933-1943) 141, 142, 145, etc., respectively. The equivalents that have been used are shown in the following tabulation.

TABLE II. YEARLY VARIATION IN MATERNAL MORTALITY RATES (PER 10,000 LIVE BIRTHS) FROM 1933 TO 1951

CODE NUMBER	CAUSES OF DEATH	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944- 1946	1947	1948	1949	1950	1951
66	Total	27.2	27.9	26.0	25.6	25.0	25.3	25.3	24.0	21.6	20.5	20.0	16.8	16.5	17.1	17.1	17.1	17.1
141	Accidents during pregnancy	2.5	2.8	2.7	2.7	2.3	2.3	2.4	2.5	1.9	2.2	2.2	2.8	3.0	3.0	-	-	0.5
142	Abortion without puerperal fever	1.1	1.2	1.1	1.1	0.9	0.8	0.9	0.9	0.7	0.8	0.8	1.1	1.0	1.0	-	-	-
143	Ectopic gestation	1.3	1.5	1.5	1.5	1.4	1.3	1.5	1.5	1.2	1.3	1.3	1.2	1.3	1.4	-	-	-
67	Other disturbances	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.5	0.7	0.6	-	-	-
68	Hemorrhage	6.4	6.4	6.0	5.9	5.8	6.2	6.3	6.6	6.0	5.3	5.5	4.2	4.0	4.2	4.8	4.7	4.7
140	Puerperal fever	7.0	6.7	6.2	6.3	6.0	5.5	4.9	4.1	3.4	3.0	3.0	2.7	2.2	2.1	1.5	0.8	0.8
145	Abortion with puerperal fever	0.1	0.2	0.2	0.1	0.3	0.2	0.1	0.1	0.1	0.2	0.2	0.5	0.5	0.6	0.4	-	-
69	Puerperal fever	6.8	6.6	6.1	6.1	5.7	5.3	4.8	3.9	3.3	2.8	2.8	2.2	1.8	1.4	1.1	-	-
146	Toxemias of pregnancy	7.9	8.3	7.8	7.8	7.6	8.3	8.6	8.0	7.6	7.5	6.9	4.7	5.4	5.8	5.9	5.9	5.9
147	Albuminuria and eclampsia	6.2	6.8	6.5	6.5	6.6	7.3	7.8	7.5	7.1	7.1	6.5	4.2	5.0	5.2	-	-	-
70	Other toxemias	1.8	1.4	1.3	1.2	1.0	1.1	0.8	0.5	0.5	0.4	0.5	0.5	0.5	0.6	-	-	-
148	Other diseases	3.5	3.8	3.2	3.0	3.2	3.1	3.1	2.8	2.7	2.5	2.4	2.3	1.9	2.0	-	-	5.1
148	Puerperal embolism and sudden death, phlegmasia alba dolens	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	-	-	-
149	Other disturbances	3.3	3.6	3.1	2.9	3.1	2.9	3.0	2.7	2.6	2.4	2.4	1.7	1.3	1.2	-	-	-
150	Other concomitant diseases	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.6	0.5	0.8	-	-	-

CODE NUMBER FROM  
THE FIFTH REVISION

141  
142  
143  
144  
140  
145  
146  
147  
148  
149  
150

=  
=  
=  
=  
=  
=  
=  
=  
=  
=  
=

CODE NUMBER FROM THE  
FOURTH REVISION

141  
142  
145  
143, 146  
140  
145, 147 a, b  
146, 144 a, b, 148 a, b, c  
144 c, d, e, 148 d, e  
147 c, d  
149  
150

As is noted in Table II, the mortality rates show toxemias of pregnancy to be the chief causes of death and hemorrhage and puerperal infection to be next in succession except in years prior to 1937. Other causes were of little significance.

**MATERNAL MORTALITY RATES  
BY THREE LEADING CAUSES**

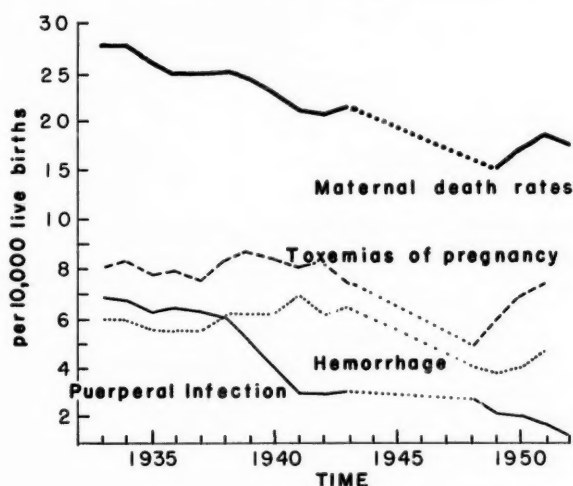


Fig. 3.

It should be remarked in particular that the incidence of puerperal embolism and sudden death or phlegmasia alba dolens including thrombophlebitis is extremely low in Japan, unlike the situation in the United States and European countries.

Thus it can reasonably be said that toxemias of pregnancy, hemorrhage, and puerperal infection are the complications which account for the greater part of the maternal deaths.

*C. Yearly variation in maternal mortality rates from three outstanding causes, toxemias of pregnancy, hemorrhage, and puerperal infection, from 1933 to 1951:*

To make the yearly variation in maternal mortality rates from three leading causes more marked, sections concerned are separated from Table II and listed or graphically shown in Fig. 3.



Noteworthy here is the remarkable reduction in the maternal mortality rates from puerperal infection during the past two decades from 7.0 in 1933 down to 0.8, approximately one-ninth that rate, in 1951. As to the mortality rates from the other two causes, no noticeable yearly variation is observed except in those from the toxemias of pregnancy which show rather a slight upward trend since 1947. It is not too much to say that the yearly decline in deaths due to puerperal infection almost accounts for the entire improvement in the total maternal mortality rates.

*D. Yearly variation in maternal deaths from three major causes with analysis of each cause from 1947 to 1949:*

What has been mentioned previously is also noted in the yearly variation in maternal deaths from three major causes as well as the subordinate causes of each from 1947 to 1949 (Table III). Some additional comments will be made here on the incidence of each cause, together with some countermeasures. It is to be noted that premature separation of the placenta has been included under hemorrhage in accordance with the International Statistical Classification, although of late many regarded it as belonging to the toxemias of pregnancy.

TABLE III. YEARLY VARIATION IN MATERNAL DEATHS FROM THREE LEADING CAUSES FROM 1947 TO 1949

CAUSES OF DEATHS	1947	1948	1949
<i>Toxemias of Pregnancy.—</i>			
Total	1,307	1,474	1,569
141 a	26	10	4
141 c	23	14	9
144 a, 148 a, b	726	819	839
	(2.71)*	(3.05)*	(3.11)*
144 b, 148 c	386	509	568
144 c, 148 d	19	11	19
144 d	59	47	57
144 e, 148 e	68	64	73
<i>Hemorrhage.—</i>			
Total	1,926	1,811	1,833
141 b	40	48	44
142 b	312	331	340
143 a, 146 a	212	187	208
143 b, 146 b	339	358	348
146 c	251	249	321
143 c, 146 d, e	327	280	250
149 a, b, c	445	358	322
<i>Puerperal Infection.—</i>			
Total	770	632	595
140 a, b, c, d, e	135	128	174
142 a	14	16	26
147 a, b, c, d	621	488	395

\*Rate per 10,000 live births.

1. *Toxemias of pregnancy:* Among the toxemias of pregnancy, eclampsia (144 a, 148 a, b) shows the highest incidence every year, followed by albuminuria and nephritis (144 b, 148 c). Eclampsia alone almost accounts for the yearly increase in the maternal deaths from toxemias of pregnancy in general.

That the cases of eclampsia itself showed a downward trend from 1941 to 1946 and thereafter, during most of which period the Pacific War was being waged, was pointed out by me at the International and Fourth American Con-

gress on Obstetrics and Gynecology held in New York City, May, 1950. How can it be explained that maternal deaths from toxemias have rather shown a gradual increase in number since 1947? It may possibly be attributed to the increase in the number of cases of eclampsia resulting from the increased intake of animal proteins and fat following the end of the war.

In order to reduce the maternal mortality rates from eclampsia it is of the utmost importance not only to ensure the early diagnosis and treatment of its three principal symptoms, edema, hypertension, and albuminuria, by persuading expectant mothers to make properly spaced visits to a physician during pregnancy, but also to increase the general concern for the possible dangers of childbirth by making delivery in the hospital much more popular than at present.

#### AGE DISTRIBUTIONS OF MATERNAL MORTALITY RATES BY THREE LEADING CAUSES DURING 1949

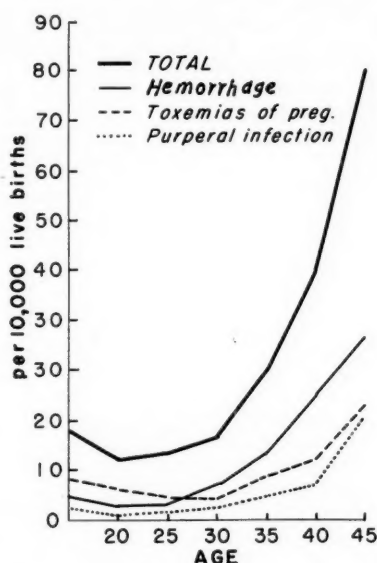


Fig. 4.

2. *Hemorrhage*: Hemorrhage is also an important complication causing 1,926, 1,811, and 1,833 maternal deaths, respectively, during the years being reported.

Hemorrhage in childbirth is usually an unexpected accident. In only a few cases, such as in habitual atonic bleeding caused by congenital poor development of the uterine musculature or premature separation of the placenta as a kind of toxemia of pregnancy, is it predictable to some extent. Thus it is on the possibility of hemorrhage that the necessity of hospitalization for childbirth is centered. Hospitalization alone assures expectant mothers the attention of attending physicians or well-trained midwives with the necessary first aid measures to meet emergencies.

3. *Puerperal infection:* As has been stated previously, maternal mortality rates from puerperal infection showed a tremendous reduction during the past two decades, from 7.0 in 1933 down to 0.8, approximately one-ninth that rate, in 1951. This reduction is also observed in the changes from 1947 to 1949. In all likelihood this improvement is ascribable to the widespread preventive as well as curative use of the sulfonamides and antibiotics. I am confident such reduction will be increased by the further application of such treatment, particularly by the routine preventive use of chemotherapy prior to or following childbirth, regardless of the absence of signs of infection.

*E. Age distribution of maternal deaths and mortality rates (per 10,000 live births) from three leading causes during 1949:*

The age distributions of maternal deaths and mortality rates from three leading causes during 1949 are graphically demonstrated in Fig. 4.

The age-specific maternal mortality rate as a whole in the age group 20 to 24 years is 11.7, the lowest of all age groups, followed by 12.0 and 16.7 in the age groups 25 to 29 years and 30 to 34 years, respectively, on one side, and 17.1 in the age group under 20 years on the other. From 35 years of age on it rises abruptly to become 2.5 times (30.0), 4.5 times (50.6) as well as even 8 times (90.0) as high as the lowest rate in the age groups 35 to 39 years, 40 to 44 years, and beyond 45 years, respectively. Thus it has been revealed that the maternal mortality rate as a whole is closely associated with the age of the mother, the safest childbearing age lying between 24 and 29 years. On the other hand, it should be noted that the danger of childbearing becomes exceedingly high beyond 35 years of age and continues to rise in accordance with the advance in age of the mother, while it is also relatively high (17.1) in the age group under 20 years of age.

The tremendous increase in mortality rate with advancing years may presumably be explained, in addition to the unavoidably increasing incidence of obstetric causes themselves, on the basis of the rise in frequency of some factors closely connected with the obstetric causes, and therefore likely to complicate gestation, such as hypertension, various kinds of genital hemorrhagic disorders, etc., while the relatively high rate in the years under 20 may be attributed to some extent to dystocias due to prematurity of the reproductive organs as in young primigravidas.

To be exact, the age-specific maternal mortality rate from the toxemias of pregnancy is lowest (4.6) in the age group 25 to 29 years, next high (4.8) in the age group 30 to 34, followed (5.4) by that in the age group 20 to 24 years, respectively, although no notable variation is to be observed in each rate. That the age-specific maternal mortality rate from toxemias of pregnancy rises extremely high beyond the age of 35 is also noted here just as in the case of the age-specific maternal mortality rate as a whole previously described.

Hemorrhage has its lowest age-specific maternal mortality figure (3.0) in the age group 20 to 24, and its gradual rise is also observed with increase in age similar to that in the case of the toxemias of pregnancy.

As regards the age-specific maternal mortality rate from puerperal infection, it is the lowest (1.8) in the age groups 20 to 24, 25 to 29, and 30 to 34,

while its abrupt increase beyond the age of 35 is similar to that in the toxemias of pregnancy.

*F. Maternal deaths and mortality rates (per 10,000 total births) by prefecture, city, and county during 1950:*

Maternal mortality rates show a considerable variation in different parts of Japan. While Ehime Prefecture enjoyed a rate of only 12.1, the corresponding figure for Nara Prefecture was 24.1, the average rate for all the prefectures being 15.7.

As regards the variation by city and county, the number of women who died in cities in 1949 as the direct result of childbearing was 1,491 in 1,002,544 total births (14.9 deaths per 10,000 total births), whereas in counties it was 3,110 in 1,886,770 total births (16.5 deaths per 10,000 total births). In other words, there were twice as many maternal deaths in counties as in cities, despite the fact that the number of the total births in counties failed to double those in cities.

Such geographic differences in maternal mortality rates may probably be attributable to the cultural or intellectual advancement, health education, or environmental conditions characteristic of each area, particularly the expansion of ideas favoring maternal welfare.

In particular, the prefecture-specific maternal mortality rates from the toxemias of pregnancy were distributed from 9.1 in Fukui Prefecture to 3.4 in Kyoto Prefecture. During the years from 1933 to 1938 they amounted to 12.29 in large cities with a population of over 100,000, whereas they were only 6.29 in other cities with smaller population or rural areas, the former, therefore, being twice as high as the latter. The same was also true during 1949, although the difference between the two groups was considerably decreased, the former and the latter being 5.30 and 4.32, respectively. The reasons why the maternal mortality rates from the toxemias of pregnancy in big cities are higher than those in smaller cities or rural areas are not evident so far.

The prefecture-specific maternal mortality rate from hemorrhage has its highest rate (7.1) in Akita Prefecture, and lowest rate (2.1) in Kyoto Prefecture. Both Akita and Nara (6.9) Prefectures are noted also for their high maternal mortality rates from hemorrhage.

TABLE IV. MATERNAL DEATHS AND MORTALITY RATES FROM PUERPERAL INFECTION IN CITIES AND COUNTIES DURING 1949 (PER 10,000 TOTAL BIRTHS)

CODE NUMBER	CAUSES OF DEATH	ALL JAPAN		CITIES		COUNTIES	
		NUMBER	RATE	NUMBER	RATE	NUMBER	RATE
140	Abortion with mention of infection (gestation of 7 months or less)	174	0.60	62	0.62	112	0.59
147	Infection during childbirth and the puerperium (gestation of 8 months or over)	395	1.37	107	1.07	288	1.53
Total		569	1.97	169	1.69	400	2.12

Concerning the rates from puerperal infection, they are highest in Aomori Prefecture (4.6) and lowest in Shizuoka Prefecture (0.3), the mean rate of all the prefectures being 1.3. On the other hand, the difference between the



maternal mortality rate from puerperal infection in cities and that in counties during 1949 is clearly indicated in Table IV, the latter (2.12) being much higher than the former (1.69).

The relatively high rates of maternal mortality in Aomori and Iwate (4.4) Prefectures, as may be supposedly the case in any uncivilized area, may possibly be ascribable to the conventional unlawful means resorted to in childbirth, or unhealthful surroundings in which women are placed at the time of childbearing.

### Comment

What have been described here are statistics concerning maternal deaths or mortality rates in Japan on the basis of the International Statistical Classification dealing only with those due to special obstetric causes. Attention must be called to the fact that there is another group of maternal deaths, that is to say those caused by general nonobstetric diseases, for example, tuberculosis, pneumonia, heart disease, hypertension, uterine neoplasms, etc., which are inclined as a rule to become more serious when associated with pregnancy, childbirth, or the puerperium. It must be recalled, therefore, that maternal deaths as well as mortality rates in Japan would actually be far greater than those demonstrated in the statistical data previously mentioned.

### Conclusions

In Japan there has been observed a considerable reduction in maternal mortality rates during the past five decades from 39.8 to 15.5 per 10,000 total births, or approximately two-fifths the rate fifty-two years ago.

One should not, however, be content with the present state of affairs. Further improvement should be achieved by any means. Particular efforts are required now that the rates have remained practically stationary at the level of 15 deaths per 10,000 births without a declining trend during the four years since 1948. To meet the situation, every effort should be made to improve antenatal or postnatal care, to increase hospitalization for birth as well as to expand the preventive routine administration of chemotherapy prior to or following childbirth. In short, health education and the general program for maternal welfare must be expanded as energetically as possible. By so doing there will no doubt be a reduction not only in special obstetric causes of maternal deaths, particularly three major conditions, toxemias of pregnancy, hemorrhage, and puerperal infection, but also in general nonobstetric diseases, such as tuberculosis, pneumonia, or heart disease, which are likely to show unfavorable progress when associated with pregnancy, childbirth, or the puerperium, and are therefore none the less significant as causes of maternal death.

I am indebted to Dr. Yukio Tanami, Chief of the Maternal and Child's Health Section, Children's Bureau, Ministry of Health and Welfare, for his courtesy in making the statistical data of the Ministry available for this paper, and also to Professor Mitsuo Segi Ex-Chief of that Section, for his kind suggestions for this work.

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## FETAL MORTALITY\*

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THE rather remarkable reduction in perinatal mortality in recent years from a more or less static figure of around 4 per cent to little more than 2 per cent in some clinics at the present time is very gratifying. This improvement has, however, been only partially explained. Several analyses have covered the question of duration of pregnancy (fetal size), and specific causes of death. Others have dealt more with the time of death relative to labor, and specific causes of death. In the hope that an approach to the problem dealing with all three factors, fetal size, relationship to labor, and specific causes of death, might yield more information, the present study was undertaken. It was our hope that in addition to learning more about why perinatal mortality had been decreased, we might also find at least part of the answer as to how to reduce present figures further.

It is, perhaps, presumptuous to present such a study from a small clinic which has gradually increased from some 800 deliveries a year to some 1,500. It was felt, however, that since all of these cases had been carefully documented, and that a constant effort had been made to determine the cause of death, and that certain improvements had occurred as a result of that effort, the small number of 13,961 consecutive deliveries, with a total wastage of 478 fetuses and infants, might prove sufficient for a simple analysis. This group was divided into an "earlier" series of 7,085 and a "later" series of 6,876. It should, perhaps, be further mentioned that our material is roughly half Negro and half white, 20 per cent private and 80 per cent clinic. In the earlier series, something over 80 per cent were "booked" cases, and in the later series well over 90 per cent were our own patients.

In the earlier series, there were 101 patients whose babies weighed between 1,000 and 1,495 grams. In the later series, only 60. This lower incidence of immature infants must be credited to a general improvement in obstetric care in our community rather than to any effort on the part of our own clinic. It will be seen from Table I that the greatest loss of life in this group is due to toxemia of pregnancy and/or premature separation of the placenta. These two complications have been grouped together in these first tables because it is sometimes impossible to tell whether the death has been due to the toxemia per se or to the premature separation. The fact that the deaths attributed to toxemia have seemingly decreased and those attributed to premature separation have seemingly increased would apparently reflect a better type of prenatal care. Again, this improvement should be attributed more to the general com-

\*Presented at a meeting of the Chicago Gynecological Society, Dec. 18, 1953.

munity than to the work done in our own clinic. The apparent increase in gross fetal anomalies is, I am sure, due to better and more careful work relative to postmortem examination by our pathologists. I feel very sincerely that pathologists the country over were most careless of postmortem examinations of the premature, macerated infant. Dr. Edith Potter, perhaps more than anyone else, should receive the credit for the considerable improvement in this regard in recent years. I am quite sure that a number of gross fetal anomalies inconsistent with life are still being overlooked. I would further like to call attention in Table I to the number of deaths which we must still label as "unknown." A constant and persistent effort has been made to induce house officers to obtain autopsies on all stillborn infants and those who die in the neonatal period, and the percentage of postmortems so obtained is quite satisfactory. All too frequently, however, in our earlier series such fetuses, particularly if quite immature, were treated as "surgical specimens," and a complete autopsy was not performed. Only very gradually have we been able to overcome this apathy in the Pathology Department. Our greatest success has, perhaps, come since there has been instituted an interdepartmental conference between pediatrics, obstetrics, and pathology, wherein some of these cases are analyzed as an exercise for the senior class. Students are very much interested, take a very active part in these discussions, and, since the pathologists must participate, they no longer like to come empty handed. We are still failing of our goal in that not every such loss of life is being so discussed. It is our hope (Pediatrics and Obstetrics) so to analyze every single such case within the next year, no matter how immature the fetus nor how obvious the cause of death.

TABLE I. FETAL MORTALITY (1,000-1,495 GRAMS)

EARLIER SERIES (101)		% OF DEATHS	LATER SERIES (60)		% OF DEATHS
Anomalies	3	5	Anomalies	6	15
Toxemia	20	25	Toxemia	3	11
Premature separation	5	45	Premature separation	8	28
Placenta previa	2	4	Placenta previa	1	3
Other placenta	0		Other placenta	2	5
Trauma	1	2	Trauma	4	10
Firm cervix + long labor	0		Firm cervix + long labor	0	
Prolapsed cord	1	2	Prolapsed cord	0	
Syphilis	4	7	Syphilis	0	
Other infections	3	5	Other infections	2	4
Diabetes	0		Diabetes	0	
Erythroblastosis	0		Erythroblastosis	0	
Hyaline membrane	8	14	Hyaline membrane	5	13
Miscellaneous	2	4	Miscellaneous	2	5
Unknown	6	11	Unknown	6	15
	55	99%		39	98%

Table II shows our losses of infants that weighed between 1,500 and 2,495 grams. Here again, the principal cause of death is the combination of toxemia and premature separation. The higher percentage of gross anomalies and hyaline membrane reflects a more careful study of these deaths by the Pathology Department. The still high percentage of unknown causes detracts materially



from the reliability of the specific causes of death, and indicates the still imperfect system under which we are working.\*

TABLE II. FETAL MORTALITY (1,500-2,495 GRAMS)

EARLIER SERIES (620)			% OF DEATHS	LATER SERIES (597)			% OF DEATHS
Anomalies		6	5	Anomalies		9	16
Toxemia	20}	33	28	Toxemia	9}	15	26
Premature separation	13}			Premature separation	6}		
Placenta previa		11	9	Placenta previa		2	4
Other placenta		8	7	Other placenta		2	4
Trauma	7}	8	7	Trauma	2}	2	4
Firm cervix + long labor	1}			Firm cervix + long labor	0}		
Prolapsed cord		3	3	Prolapsed cord		1	2
Syphilis		8	7	Syphilis		3	5
Other infections		11	9	Other infections		3	5
Diabetes		5	4	Diabetes		0	
Erythroblastosis		1	1	Erythroblastosis		1	2
Hyaline membrane		9	8	Hyaline membrane		11	19
Miscellaneous		2	2	Miscellaneous		3	5
Unknown		12	10	Unknown		5	9
		117	100			57	101

Table III shows the loss of infants that weighed between 2,500 and 3,995 grams. Although the over-all death rate in this group has been halved, the proportion of deaths due to the principal causes in the other groups remains about the same—anomalies, toxemia, and “unknown” still rate very high. There now comes into the picture a high percentage of deaths due to trauma. As will be seen, this figure is materially increased by including as traumatic deaths which occurred in patients with firm cervix and prolonged labor, a problem recently discussed elsewhere. We feel that this inclusion is entirely justified, and that many babies now being lost can be saved by closer attention to this rather uncommon but, to us, very important complication of labor.

TABLE III. FETAL MORTALITY (2,500-3,995 GRAMS)

EARLIER SERIES (6,044)			% OF DEATHS	LATER SERIES (5,909)			% OF DEATHS
Anomalies		16	12	Anomalies		6	11
Toxemia	9}	14	11	Toxemia	3}	10	18
Premature separation	5}			Premature separation	7}		
Placenta previa		8	6	Placenta previa		0	
Other placenta		8	6	Other placenta		6	11
Trauma	9}	19	14	Trauma	3}	11	20
Firm cervix + long labor	10}			Firm cervix + long labor	8}		
Prolapsed cord		8	6	Prolapsed cord		0	
Syphilis		2	2	Syphilis		2	4
Other infections		10	8	Other infections		4	7
Diabetes		5	4	Diabetes		0	
Erythroblastosis		3	2	Erythroblastosis		5	9
Hyaline membrane		8	6	Hyaline membrane		3	5
Miscellaneous		6	5	Miscellaneous		2	4
Unknown		15	11	Unknown		7	12
		132	103			56	101

Coming to the babies that weighed 4,000 grams and over (Table IV), we have only a very small series of 320 patients in each of our groups. Our figures

\*“Other placenta” refers to complete placental infarction, very tiny placentas, etc.

are, therefore, not thoroughly dependable. It appears, nevertheless, that we should be able to prevent deaths from toxemia in this range. It also seems that closer attention to the avoidance of traumatic deliveries is especially important in this group of patients.

TABLE IV. FETAL MORTALITY (4,000 GRAMS OR OVER)

EARLIER SERIES (320)		% OF DEATHS	LATER SERIES (320)		% OF DEATHS
Anomalies	1	4	Anomalies	1	12
Toxemia	2}	16	Toxemia	2}	38
Premature separation	2}		Premature separation	1}	
Placenta previa	0		Placenta previa	0	
Other placenta	0		Other placenta	0	
Trauma	5}	39	Trauma	1}	12
Firm cervix + long labor	5}		Firm cervix + long labor	0}	
Prolapsed cord	1	4	Prolapsed cord	1	12
Syphilis	2	8	Syphilis	0	
Other infections	0		Other infections	0	
Diabetes	3	12	Diabetes	1	12
Erythroblastosis	0		Erythroblastosis	0	
Hyaline membrane	0		Hyaline membrane	0	
Miscellaneous	4	16	Miscellaneous	1	12
Unknown	1	4	Unknown	0	
	26	103		8	98

*Breech and "All Other" Presentations.*—While the mortality in breech presentation is moderately higher in our clinic than that for occiput presentations, and the mortality of "all other" presentations is considerably higher, it is our distinct feeling that the increased mortality is frequently due to associated pathology, such as placenta previa, fibroids, etc., or to the method of management. There has not been a single death from breech presentation in a primipara in our more recent series. Admittedly, the aftercoming head is quite subject to trauma in the immature baby and to a less extent in the markedly premature one. The higher mortality in twin pregnancy is readily explainable in our experience on the basis of specific causes unrelated to the multiple pregnancy, except for the higher incidence of toxemia of pregnancy in multiple pregnancy and, rarely, premature separation of the placenta after the birth of the first baby.

*Antepartum Deaths.*—In general, it seems to us that the three principal causes of antepartum deaths are toxemia of pregnancy, syphilis, and "other placental causes." Premature separation of the placenta produces about an equal number of antepartum deaths, on the one hand, and intrapartum and postpartum deaths on the other hand.

*Intrapartum and Postpartum Deaths.*—All other causes of death, except placenta previa (from which we have lost only three babies in our later series), appear to manifest themselves predominantly either during or following labor. This is well recognized in the case of infection, erythroblastosis, hyaline membrane, prolapse of the cord, and trauma.

If we examine our experience with each specific cause of death as to the time in pregnancy at which it took place and also the time of death with reference to labor, it seems to us likely that the way can be pointed for further reduction in our fetal mortality.

Table V has to do with the gross developmental anomalies inconsistent with life. It should be noted that, with a single exception, there is no antenatal mortality in mature babies in either series. Four in the earlier series and nine in the later series, among the immature and premature babies who had gross developmental anomalies, were said to have died from this cause before the onset of labor. It is difficult to understand how these pregnancies could have advanced as far as they did and then the fetuses should suddenly die, unless some other cause was present. It appears wise, in the case of an antepartum death where a gross developmental anomaly is found to be present, to search further for other possible causes of the wastage.

TABLE V. GROSS DEVELOPMENTAL ANOMALIES

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	2	1	6	1
1,500-2,495 grams	2	4	3	7
2,500-3,995 grams	1	15	0	6
4,000 grams and over	0	1	0	1
Total	5	21	9	15

TABLE VI. TOXEMIA OF PREGNANCY

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	10	10	2	1
1,500-2,495 grams	12	8	4	1
2,500-3,995 grams	4	5	1	2
4,000 grams and over	1	1	2	0
Total	27	24	9	4

Table VI shows the figures for toxemia of pregnancy where no premature separation was diagnosed or where it was considered a secondary and probably unimportant cause. (We have in this study, perhaps erroneously, ascribed each death to a single cause even though several possible causes of death are quite obvious.) It is particularly apparent in the later series that, even in immature and premature babies, most of the mortality occurs when delivery of the baby is too long delayed. The two intrapartum and postpartum deaths in mature babies can also probably be ascribed to the fact that too much damage was done before steps were taken to induce or to terminate labor. While a number of these antepartum deaths occurred before the patient came under our supervision, several of them occurred in the hospital while someone was waiting for the baby to become a little more mature. It is our present belief that with a toxemia patient in the hospital under medical management steps should be taken toward delivery whenever medical management fails to provide *continuous* improvement or definite signs of toxemia have been present for as much as three weeks, and *immediate* action should be taken if there is not definite

improvement within twenty-four hours or the toxemia is progressing rapidly. In the latter case, twenty-four hours should not be allowed to elapse. (We are much indebted to Dr. Frederick H. Falls for teaching us this latter point.) Not many of these babies will gain much in either weight or maturity, and more prompt intervention seems definitely indicated.

Premature separation of the placenta (Table VII) leaves us in considerable of a quandary. Admittedly, nothing can be done for those patients whose separation is sufficiently marked to produce death before we see them. Our one hope of improving the situation is among those individuals whose babies are still alive at the time the diagnosis is made. We are told that conservative therapy is to be preferred, but two of the eleven deaths in our later series could very definitely have been prevented had something more than laissez-faire been chosen for those patients. At one time, it was our opinion that if we could get these babies delivered alive they would be quite unlikely to die. We can no longer support such a contention. On the other hand, a partial separation not immediately endangering the baby may well become more marked or even complete at almost any time. I cannot help but believe that the trend of treatment of premature separation in the future will be toward more prompt delivery.

TABLE VII. PREMATURE SEPARATION

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	3	2	4	4
1,500-2,495 grams	5	8	4	2
2,500-3,995 grams	3	2	3	4
4,000 grams and over	1	1	0	1
Total	12	13	11	11

Placenta previa (Table VIII) shows what appears to be remarkable improvement in our later series. We do assume particular credit for this, but ascribe it to the fact that intrauterine bags have been completely discarded except for the occasional control of hemorrhage in the patient whose labor is progressive, and the complete elimination of combined podalic version as a means of delivery for this abnormality.

TABLE VIII. PLACENTA PREVIA

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	2	0	1
1,500-2,495 grams	3	8	1	1
2,500-3,995 grams	3	5	0	0
4,000 grams and over	0	0	0	0
Total	6	15	1	2

The improvement in the results in diabetic patients (Table IX) is, we think, due to improved prenatal care (no estrogens), and the more frequent use of



cesarean section in the case of giant babies. The one death in our later series should probably have been ascribed to trauma rather than diabetes, as it was a definite case of shoulder dystocia.

TABLE IX. DIABETES

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	0	0	0
1,500-2,495 grams	4	1	0	0
2,500-3,995 grams	3	2	0	0
4,000 grams and over	1	5	0	1
Total	8	8	0	1

Syphilis (Table X) is still a factor in fetal mortality, although the five deaths in our later series were, in all but one patient, unbooked cases. This patient had a negative serologic test at four months when first seen. A second serologic test was ordered at seven months, but was reported positive in high titer three days after the death of the baby at seven months.

TABLE X. SYPHILIS

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	3	1	0	0
1,500-2,495 grams	4	4	3	0
2,500-3,995 grams	2	1	2	0
4,000 grams and over	2	0	0	0
Total	11	6	5	0

TABLE XI. OTHER INFECTION

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	1	0	2
1,500-2,495 grams	2	9	0	3
2,500-3,995 grams	3	7	2	2
4,000 grams and over	0	0	0	0
Total	5	17	2	7

Infection of the placenta and the baby can occur with intact membranes, but in almost all instances (all in this series) it results because of premature rupture of the membranes. The nine deaths from this cause in our later series occurred in several hundred cases of premature rupture and cannot, therefore, justify radical therapy for premature rupture of the membranes. It does seem admissible that prophylactic antibiotic therapy be instituted, preferably with the broad spectrum antibiotics. Whether the moderately vigorous attempts at induction of labor, such as by intravenous Pitocin, are advisable is still a matter

of individual opinion. We are not convinced that such efforts should be made in all cases.

Trauma still takes too great a toll of infant life. We have included in these figures an entity which we regard as definitely traumatic. I refer to the coincidence of firm cervix and first stage of more than thirty hours, with failure of the cervix to soften as labor progresses and the failure of improved labor pains by the time 6 cm. dilation has been reached. Admittedly, this is an uncommon situation, but the death rate under these circumstances, as reported elsewhere, can be as high as 36 per cent.\* In addition, then, to the avoidance of combined podalic version, difficult midforceps, and studied management of midpelvic contraction, we suggest special therapy for firm cervix and prolonged labor under the circumstances described. While Dührssen's incisions can occasionally be employed successfully, particularly if they are not followed by the immediate application of forceps, we prefer, in the majority of these patients in whom the head is still at a fairly high station, to employ cesarean section. We are not yet able to predict the future role of intravenous Pitocin in this particular situation. Our limited experience with paravertebral block is encouraging as of the present. Artificial rupture of the membranes may occasionally solve the problem. The results are highly variable. We feel the procedure contraindicated with a high station.

TABLE XII. TRAUMA

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	1	0	4
1,500-2,495 grams	0	8	0	2
2,500-3,995 grams	0	19	0	11
4,000 grams and over	0	10	0	1
Total	0	38	0	18

TABLE XIII. PROLAPSED CORD

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	1	0	0
1,500-2,495 grams	0	3	0	1
2,500-3,995 grams	0	8	0	5
4,000 grams and over	0	1	0	1
Total	0	13	0	7

Prolapse of the cord will occur spontaneously very rarely before rupture of the membranes. While it can occur with spontaneous rupture of the membranes, it seems to be more frequent with artificial rupture of the membranes. If delivery can be effected promptly after either spontaneous or artificial rupture of the membranes, death is not likely to occur. If, however, considerable time

\*As high as 81 per cent according to McCain, Anderson, Lester, and Pilkington: J. A. M. A. 153: 695, 1953.

clapses, the mortality will inevitably be high. The idea of holding the presenting part (head or breech) up out of the pelvis until such time as cesarean section can be done is intriguing, but it seems doubtful that it will ever be the complete answer to this problem. We rupture the membranes artificially rather frequently, but only under restricted circumstances, or for very definite indications. The restricted circumstances are (1) desultory labor with a low station and the head well fitted into the cervix; (2) elective induction in the multipara with 4 or more cm. dilation, particularly when she lives at a distance. Definite indications for the induction of labor are severe toxemia, premature separation of the placenta, and placenta previa.

Other placental causes of death include such items as large red infarctions of the placenta in addition to previously present multiple white infarctions. We also believe that there is such an entity as placental insufficiency. A recent patient, known to be 270 days pregnant, ceased to feel fetal movements and went into labor six days later. The placenta weighed 160 grams and the fetus 1,200 grams. It is difficult to understand how this fetus could have survived as much as 270 days, with such an inadequate placental volume. It would be very desirable if we could diagnose this situation sufficiently early to get these babies delivered before they die, as we have had no deaths due to this cause in either series during or after delivery. In a previous communication, we stated that postmaturity was not to be feared because of increasing size of the baby. We were thinking then particularly of the situation where the baby was already large or of average size. Perhaps we should modify our previous conclusions to say that postmaturity may well be feared when the baby (and therefore almost certainly the placenta) is quite small. The fact that there have been no deaths from placental causes in either series when the baby was large seems to substantiate this idea.

TABLE XIV. OTHER PLACENTA

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	0	2	0
1,500-2,495 grams	8	0	1	0
2,500-3,995 grams	8	0	2	0
4,000 grams and over	0	0	0	0
Total	16	0	5	0

TABLE XV. ERYTHROBLASTOSIS

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	0	0	0
1,500-2,495 grams	0	1	0	1
2,500-3,995 grams	0	3	0	5
4,000 grams and over	0	0	0	0
Total	0	4	0	6

We do not know of a single instance of antepartum death due to erythroblastosis. As a matter of fact, we have had no deaths intra partum. Is it possible that we are wasting a great deal of our patients' money by repeated Rh and titer testings during pregnancy, when a properly performed Coomb's test or cord-blood bilirubin determination at the time of delivery will give us ample time to institute replacement transfusions or other desired therapy?

Hyaline membrane is a fantastic condition which occurs in infants delivered of perfectly normal mothers by perfectly normal labor or what is, or should be, more advantageous, cesarean section. Dr. Herbert Miller, who has written repeatedly on this subject, tells me that our grandchildren will not know the answer to this problem. Perhaps he is right. I cannot escape the conclusion that it may well be a form of gross developmental anomaly. Compare the figures in Table XVI with those in Table V, having in mind the remarks made in connection with Table V, that gross developmental anomalies probably seldom produce death before the birth of the baby.

TABLE XVI. HYALINE MEMBRANE

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	0	8	0	0
1,500-2,495 grams	0	9	0	11
2,500-3,995 grams	0	8	0	3
4,000 grams and over	0	0	0	0
Total	0	25	0	14

We have included in Table XVII more or less unusual conditions, which, in our estimation, are either definite entities or are sufficiently definite in the present state of knowledge to be causative of death. No conclusions or suggestions are offered in connection with them.

TABLE XVII. MISCELLANEOUS

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	1	1	1	1
1,500-2,495 grams	1	1	1	2
2,500-3,995 grams	3	3	0	2
4,000 grams and over	2	2	0	1
Total	7	7	2	6

We regret very much that, even in our later series, seven antepartum deaths and six deaths intra partum and post partum occurred without a definite cause of death having been found. That there were only thirteen of these as compared to thirty-four in our earlier series shows that we have improved a little in getting to the solution of this problem. The session with senior students previously referred to has been really helpful in urging the pathologists particularly to increased effort. Admittedly, the one immature infant and two



premature infants in this later series were macerated and did not offer the usual opportunity for discovering exactly what caused the baby's death. It appears that the four term infants could have been studied sufficiently well for the most probable cause of death to have been found. The six intrapartum and postpartum deaths should certainly have been explainable. In at least four of these six instances, the failure to find the cause of death was probably due to the fact that a single section or no section at all was taken from the placenta. In such cases, it is our present belief that more sections of the placenta must be taken. This means that all placentas must be preserved for at least seventy-two hours, particularly when the new baby is not doing well, in order that if he should die a more extensive placental study can be instituted. We have just now adopted a plan of procedure for all antepartum and intrapartum deaths with the additional feature (Table XIX) of a delayed (if necessary) study of the placenta.

TABLE XVIII. UNKNOWN

	EARLIER SERIES		LATER SERIES	
	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS	ANTEPARTUM DEATHS	INTRA- AND POSTPARTUM DEATHS
1,000-1,495 grams	2	4	1	2
1,500-2,495 grams	2	10	2	3
2,500-3,995 grams	4	11	4	1
4,000 grams and over	0	1	0	0
Total	8	26	7	6

Most of our previous failure of progress in this field of fetal mortality has been due to the unknowing negligence of house officers in vital details necessary to work out exact causes. This plan (Table XIX) is offered not as an answer to the problem but rather in the hope that some of you will help us in our further efforts in this direction.

TABLE XIX. THE UNIVERSITY OF KANSAS MEDICAL CENTER  
PERINATAL DEATH RECORD

Name \_\_\_\_\_ Race \_\_\_\_\_ Age \_\_\_\_\_ G. \_\_\_\_\_ P. \_\_\_\_\_ L.M.P. \_\_\_\_\_ Days Gest. \_\_\_\_\_  
Previous stillbirth or neonatal death (dates and causes) \_\_\_\_\_

Serology \_\_\_\_\_, Antileuetic R/ (Date, type & Amt.) \_\_\_\_\_

Rh \_\_\_\_\_, Antibody titers \_\_\_\_\_, Coombs \_\_\_\_\_

Blood Sugar: Fasting \_\_\_\_\_, Glucose Tol. \_\_\_\_\_ A.B.O. Group Mother \_\_\_\_\_ Fetus \_\_\_\_\_

Fetal movement last noted \_\_\_\_\_ F.H.T. last heard \_\_\_\_\_

Nutrition:

A. Wt. gain by trimester; 1st \_\_\_\_\_, 2nd \_\_\_\_\_, 3rd \_\_\_\_\_ Total \_\_\_\_\_

B. Diet with brief discussion \_\_\_\_\_

C. Hb. and R.B.C.: 1. Prenatal \_\_\_\_\_ 2. Delivery \_\_\_\_\_

Pelvic Measurements:

A. Manual: P.F. \_\_\_\_\_, P.NF \_\_\_\_\_, I.T. \_\_\_\_\_, P.S. \_\_\_\_\_, Sacrum & coccyx \_\_\_\_\_

B. X-Ray: C.V. \_\_\_\_\_, Trans. inlet \_\_\_\_\_, I.S. \_\_\_\_\_, A.P. & post. sag. Mid Pelvis \_\_\_\_\_, I.T. \_\_\_\_\_

Vaginal Bleeding:

A. Onset.

B. Estimated amt.

C. Tenderness and uterine tone assoc.

D. Clinical diag.

E. Anatomical diag.

Recent Maternal Morbidity and Pertinent Past Medical and Surgical History:

A. Heart disease

B. Tuberculosis

C. Diabetes

D. Pelvic surgery

E. Viral disease during preg.

F. Infections

G. Toxemia

1. Onset giving signs/symptoms

2. Medical treatment—date, type, and results

3. Severity

Labor Summary:

A. Length 1st stage \_\_\_\_\_ B. Length 2nd stage \_\_\_\_\_ 1. Time \_\_\_\_\_

2. No. pains: descent, floor, total \_\_\_\_\_

C. Membranes: 1. Time rupt. \_\_\_\_\_ 2. Char. fluid \_\_\_\_\_

D. Medications 1st and 2nd stage (time and amt.)

E. Analgesia and anesthesia (time and amt.)

Delivery Summary:

A. Operative

B. Trauma assoc.

C. Position

D. Complications

## Infant

- A. Wt. \_\_\_\_\_ grams      B. Length \_\_\_\_\_ cm.      C. Sex \_\_\_\_\_
- D. Gross abnormality
- E. Time of delivery to:
1. Regular breathing
  2. 1st gasp
  3. 1st cry
- F. Aspiration

## Placenta

- A. Wt. \_\_\_\_\_ grams      B. Measurement \_\_\_\_\_ cm. × \_\_\_\_\_ cm. × \_\_\_\_\_ cm.
- C. Abnormality
- D. Cord
1. Abnormality
  2. Complication

## Autopsy

- A. Consent
- B. Findings—(gross)
- C. Provisional anatomical diag.
1. \_\_\_\_\_
  2. \_\_\_\_\_
  3. \_\_\_\_\_
  4. \_\_\_\_\_
- D. Final diagnosis
- E. Multiple sections of placenta
1. Micro.
  2. Gross.

## INSTRUCTIONS

1. Information needed to complete this record is to be obtained by the obstetric resident as soon as possible.
2. The necessary signatures for autopsy consent are to be obtained immediately.
3. The obstetric resident is to be present at the autopsy to observe. Any delay between the time the permit is signed and the beginning of the autopsy is to be discouraged by the obstetric resident.
4. All stillborns are to be weighed and measured before leaving the obstetric department—also weigh and measure all liveborn infants under 2500 grams. Head, shoulder and chest measurements are to be made on all stillborns having difficulty in the second stage or weighing over 4000 grams.
5. Multiple sections are to be obtained from the placenta of all stillborn infants and all liveborn infants showing signs of distress. Placenta and sections from (a) liveborn infants are to be sent to surgical pathology, (b) stillborn infants are to be sent to the morgue with the infant.
6. On suspected cases of Rh incompatibility first obtain Rh typing of mother and infant, then maternal antibody titer and Coombs test\* if indicated. Obtain ABO typing of mother, infant and all other older children if no Rh incompatibility but clinical and laboratory evidence of hemolytic anemia.
7. Obtain a fasting blood sugar on mothers of stillborns over 4000 grams, with a diabetic family history or glycosuria; follow with a glucose tolerance test if an abnormal report returns.
8. Obtain x-ray pelvimetry on all cases of (a) questionable manual pelvimetry (b) prolonged second stage.
9. Diet history is to be obtained by the obstetric resident in detail and then give a brief summary as to adequacy or inadequacy of diet and give reasons why.
10. Positive answers under the heading recent maternal morbidity and pertinent past medical and surgical history are to be given in considerable detail.
11. The final diagnosis under autopsy heading will be filled in by the department secretary.

\*Or cord-blood bilirubin.

## A PREVILLOUS OVUM OF ELEVEN DAYS' DEVELOPMENT

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School of Medicine and Dentistry)

UP TO recent years only a very few early human ova have been available for study. Among the best known are the Peters ovum, the Bryce-Teacher and the Miller ova. The latter was first described by Miller in 1909, and was re-studied and a more adequate description given by Streeter in 1926. The Miller ovum represented the youngest human ovum described up to that time and was estimated as being of eleven days' development. Unfortunately, it was a very incomplete specimen, only five slides being available for study. This specimen remained the youngest known human ovum until the more recent studies of Hertig and Rock, who have advanced tremendously our knowledge of the early phases of human development. Their studies included one specimen as early as four days, which they felt may be abnormal, and others of seven, eight, nine, eleven, and twelve days' development, respectively. Their studies on these specimens have been very complete and fill in many gaps in our knowledge, but there are still unobserved phases remaining in the very early stages.

The ovum herewith presented was obtained from the uterus of a young married woman, aged 26 years (T. D. M., Unit No. 291666), who presented herself at the outpatient clinic of the obstetrical and gynecological department of the Strong Memorial Hospital on Feb. 8, 1949, with the complaint of failure to become pregnant.

The pertinent points in her past history are as follows. She had been married for eight years, underwent one normal full-term pregnancy seven years previously, this being followed by three early miscarriages at one to two months, the last one having occurred in June, 1948. At the time of her outpatient visit, the date of her last menstrual period was given as Feb. 4, 1949, and she followed a regular 27 to 28 day cycle. General and pelvic examination revealed no abnormalities.

On March 2, two days before her next expected menstrual period, in order to study the endometrium, an endometrial biopsy was obtained. One small tag of the tissue obtained contained the ovum, almost intact, which is herewith described. A very small fragment of the chorion laterally is missing. It is interesting to note that two days after the biopsy, on March 4, she began a normal menstrual period which lasted for four days. From the history as given, as well as by comparison with other early ova as described by Hertig and Rock, it is believed that this ovum is probably in its twelfth day of development.

### Description of Specimen

#### *Decidua.*—

There are only a few tags of endometrium available for study, as the material was obtained by biopsy and a complete curettage was not done. The glandular structures show evidence of glandular activity but this is not as marked as it probably would be a little later; in other words, the endometrium has not as yet been completely transformed into a typical decidua but is rather in the progestational phase. The compact layer of the endometrium shows a marked degree of edema (Fig. 1).



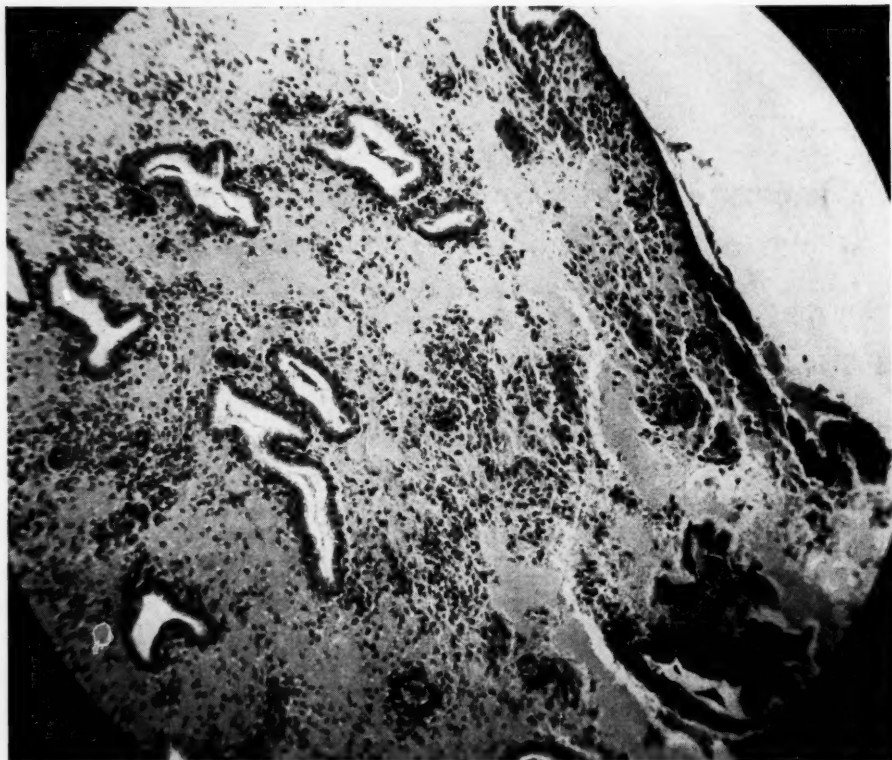


Fig. 1.—A tag of endometrium. Note the marked edema of the compact layer. The glands show activity, but the picture is not yet that of a completely developed decidua.



Fig. 2.—A low-power view of the ovum and adjacent endometrium. The ovum is completely implanted but a small gap is noticed on the endometrial surface which has not as yet been completely repaired following implantation. ( $\times 100$ ; reduced  $\frac{1}{6}$ .)

It was in a tag of this compact layer that the ovum was discovered. The ovum is implanted in this tag and lies just beneath the surface epithelium of the endometrium. The point of its entrance however has not as yet been completely repaired by growth of the adjacent endometrium.

*The Ovum (Fig. 2).—*

The measurements of the ovum are as follows: external chorion: 0.5 by 0.6 mm.; internal chorion: 0.47 by 0.24 mm. The third dimension cannot be determined as a small lateral portion of the chorion is missing. Amniotic cavity: 0.058 by 0.070 by 0.091.

*The Chorion.—*

The trophoblast presents the usual picture seen at this stage of development. Its inner portion, the cytotrophoblast, is a layer of variable thickness, in places only a single cell layer, in others, several layers. It is as thick at the abembryonic pole as at the embryonic pole. Projecting from it can be seen occasional thicker irregular processes which probably are the forerunners of true chorionic villi (Fig. 3).

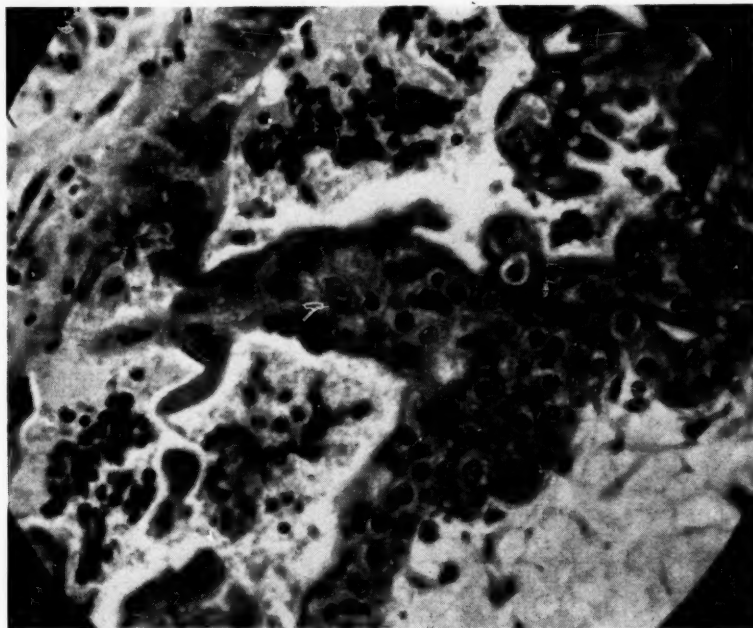


Fig. 3.—A portion of the cytotrophoblast which shows a projecting solid epithelial bud, probably the forerunner of a chorionic villus. ( $\times 160$ ; reduced  $\frac{1}{3}$ .)

The syncytiotrophoblast is represented by irregular proliferating processes presenting no division into actual cells. These form lacunae in which is observed maternal blood. The endometrium adjacent to the syncytiotrophoblast is markedly edematous and shows evidence of fibrinous degeneration—Nittabuch's fibrin layer of the later placenta. No actual villi are to be seen.

*The Amnion and Embryonic Area.—*

The amnion is represented as a tiny, enclosed cavity, at the base of which is seen the embryonic area. Laterally its wall is formed by a single layer of cells, while the wall opposite the embryonic area is formed by a two-cell layer and it lies a very short distance beneath the cytotrophoblast, at this point. Between this portion of the amnion and the cytotrophoblast, a small accumulation

Fig. 4.

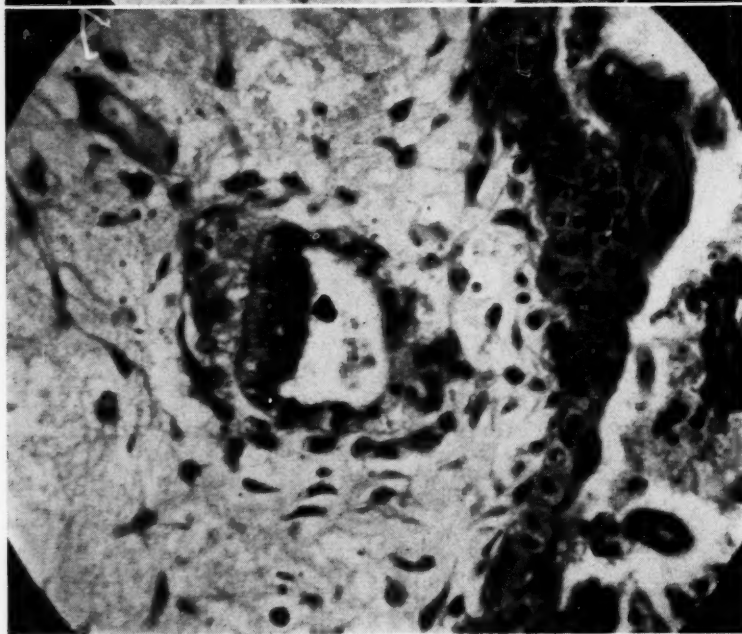
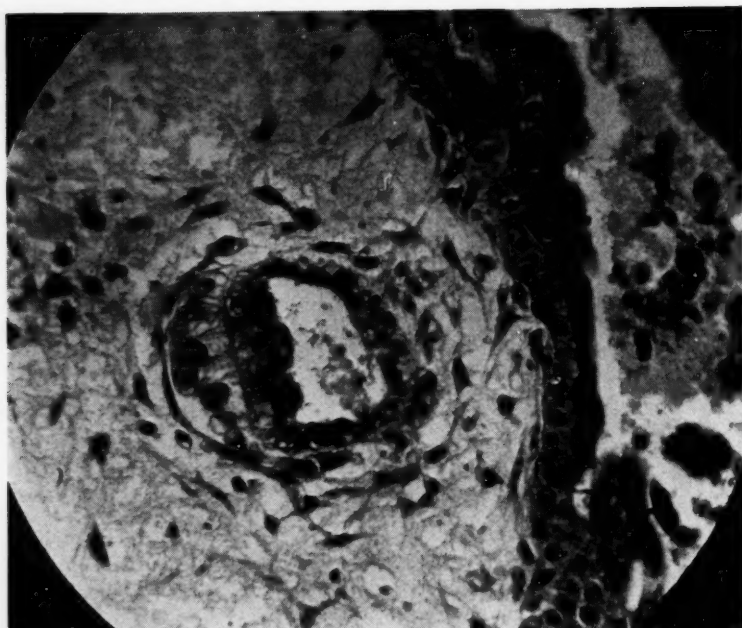


Fig. 5.

Fig. 4.—The amnion and embryonic area are shown here. Note that the amnion is laterally made of a single layer of cells, while at the abembryonic pole there are two layers. The beginning of the endoderm is noted beneath the embryonic shield, but there is as yet no yolk sac. ( $\times 160$ ; reduced  $\frac{1}{5}$ .)

Fig. 5.—A slight defect in the abembryonic portion of the amnion is noted here. It is being closed by amniogenic cells delaminated from the cytotrophoblast. ( $\times 160$ ; reduced  $\frac{1}{5}$ .)

of fibroblastic cells is noted. This probably represents the earliest stage of the Bauchstiel. These cells are apparently being delaminated from the inner layer of the cytotrophoblast (Fig. 4).

In one section (16) a small segment of the amnion at its abembryonic portion is incomplete, but a number of cells, amniogenic, can be seen extending from the overlying cytotrophoblast apparently to complete this defect (Fig. 5).

The two-cell layer of amnion adjacent to this point can probably be explained on the basis of the recent origin of the cells from the cytotrophoblast and of the fact that they have not as yet assumed the more mature arrangement seen laterally as a single layer.

The embryonic disc is represented by a rather thick layer of large, generally columnar cells. Beneath this is a rather irregular layer of polyhedral cells, the beginning of the endoderm delaminated from the embryonic disc. Mitotic figures are rather numerous in both the cells of the embryonic disc and the beginning endoderm. There is no definite yolk sac as yet.

The extraembryonic coelom is relatively large as is normally the case. It is filled with magma in which scattered cells are observed and presents a very imperfectly developed Heuser's membrane (Fig. 6).

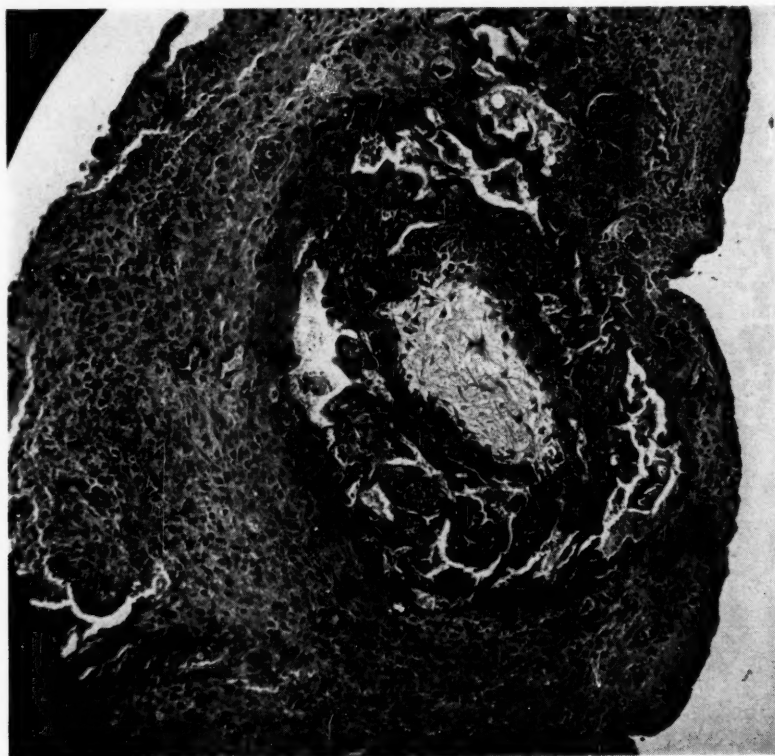


Fig. 6.—The ovum at one of the lateral poles. It is here completely covered by endometrium. A small depression is noted on the surface corresponding to the point of entrance but the endometrium is completely repaired. The plasmodi- and cytotrophoblast are seen, the former proliferating actively. The extraembryonic coelom containing magma and scattered cells is observed. ( $\times 100$ ; reduced  $\frac{1}{5}$ .)

### Summary

The specimen presented is one of an apparently normal human ovum which from menstrual history and state of development is probably just beginning its twelfth day of growth.



It compares very closely in development with one described by Hertig and Rock (Carnegie No. 7699) and presents features very similar to those of that specimen.

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## HEMODYNAMIC CHARACTERISTICS OF THE FETAL CIRCULATION

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OUR attitudes toward situations reflect our previous experiences. As a result, we simplify our problems by adopting conventional viewpoints. We bring few new insights to bear on them for the purpose of appreciating their full significance, for it is easier to rely upon the dogma of the past than it is to create a dogma for the future.

This is exemplified by our conventional thinking concerning the fetal circulation. We know that it seems paradoxical to us. Why, for example, does the fetus show prompt bradycardia in the face of circulatory distress, upon prolonged contraction of the uterus, when in adults the cardiac response is one of prompt acceleration to circulatory stress? By regarding fetal stress bradycardia as a paradox, we reveal our conventional attitude. We expect the fetus to behave like a postnatal organism, for that is our principal point of reference. Surely the paradox is created solely within our own minds since the baby within the womb does not know enough—yet—to behave paradoxically.

The proper attitude should be one which leads us to look, *de novo*, upon the fetal circulation as a physiological activity which exists to provide for the growth of the fetus. It may be expected, therefore, that the fetus possesses features that are uniquely adapted to a nonbreathing and aquatic organism of which the most vital part is the placenta. The cardinal function of the circulation of the fetus is to provide abundantly for the movement of blood through this organ until the moment of birth. Then the placenta becomes a waste product of parturition.

What approach, therefore, may an inquiring student take in order to assess anew the essential hemodynamic nature of the circulation in the fetus? One may begin by setting down the principal known facts, and on this foundation build with the new data of recent experiments. Our knowledge then may be re-evaluated and the points of uncertainty indicated. To do this will add immeasurably to our understanding of the mother and her baby.

### Known Characteristics of the Fetal Circulation

The pathways of blood flow in the fetus and the changes which they undergo at the time of birth are known. The anatomical differences between life in the fetal and the adult conditions have been known since the days of William Harvey in 1628, although anatomists of an earlier time, extending back to the days of Galen in the second century A.D., knew of one or another part of the essential differences. In terms of development, the fetus is an aquatic organism,

deriving its oxygen and sustenance from maternal blood and giving off its waste products to it, across the tissues and structure of the placenta. The newborn infant, like the older adult, derives his oxygen through his lungs and gives off his waste carbon dioxide across the tissues of the pulmonary barrier. The change-over in mode of respiratory exchange is sudden and usually complete. It depends upon extensive alteration in the course of blood flow throughout the organism. What are these adjustments?

The heart receives blood through the large veins coming to it and it distributes blood to the arterial system. There is a difference in the manner of doing this in the fetal heart as compared with the hearts of newborn and adult individuals. True, in both the fetal and adult types of heart, blood comes into the right auricle (a word meaning "ear"), or the first chamber of the heart. After birth, blood passes from the right auricle into the right ventricle ("little belly") and thence into arteries going to the lungs, where the respiratory exchange of gases is effected. The blood then returns to the left auricle of the heart and thence to the left ventricle, and so through the branching arterial system to all parts of the body.

In the fetus, the blood returning in the veins from the lower parts of the body to the heart passes in one of two directions. That which hits on one side of a recently discovered promontory of tissue (crista dividens, or "dividing crest") passes, along with blood from the head end of the animal, into the right auricle and thence to the ventricle. The blood that hits the other side of the dividing crest passes through an opening in the septum between the right and left auricles, and enters the left auricle. This blood passes in turn to the left ventricle, having by-passed the right side of the heart.

In the fetus, the blood which enters the ventricles of the heart leaves by way of the pulmonary arterial trunk from the right ventricle, and by way of the aorta, from the left ventricle. This is true in both the newborn and adult organisms as well. However, the second difference between the two types of circulations can be seen beyond this point.

About an inch from where the main pulmonary arterial trunk begins, it divides three times. Two smaller branches go to the lungs, one to the right, and one to the left. More or less between the two branches, the main pathway continues for another short distance where it joins the large aorta which arises from the left ventricle of the heart. Here, then, is a direct and major connection between the two great arterial systems of the fetus. It is known to anatomists as the ductus arteriosus.

In infants and adults, the two arterial systems from the right and left sides of the heart are separate. However, prior to, and until the moment of birth in the fetus they are joined, so that a large portion of the blood which leaves the right ventricle joins with that coming from the left ventricle. Together, the mixed stream passes to the lowermost regions of the body, where it supplies the abdominal organs and the legs. Mainly, however, it goes to the placenta through two large arteries that pass from the end of the aorta into the umbilical cord. This is the main purpose of this part of the circulation, namely,

to assure in the fetus an abundant and continuous circulation of fetal blood through the placenta where, in fetal life, processes of respiration, assimilation, and excretion vital to the fetus take place.

That blood which finds its way into the lungs of the fetus from the pulmonary artery, instead of going into the ductus arteriosus, returns to the heart through the pulmonary veins. It enters the left auricle, where, joined by the blood coming through the foramen ovale in the septum between the two auricles as mentioned above, it passes on into the left ventricle, to be discharged into the aorta.

The cardinal differences between the fetal and neonatal circulations are now clear. They are basically threefold. There is the fact (1) of the abundant and important placental circulation in the fetus; (2) of the crossover by way of the foramen ovale of blood between the two auricles or receiving chambers of the heart; and finally (3) the shunt between the two arterial systems from each side of the heart by way of the ductus arteriosus. At the moment of birth, each of these becomes nonfunctional, and the newborn organism normally breathes from that time in the adult fashion with all that this entails in readjustment of the vascular system to the altered conditions of life. These are structural and functional changes which must, and do, transpire with remarkable rapidity.

#### **Newer Knowledge of the Fetal Circulation**

To the features of the fetal circulation just described we now need to add the facts learned by recent experimentation. By doing so, we see a far more dynamic and balanced physiological mechanism which is ideally adapted to the requirements of fetal life. The new investigations have to do with (1) regional circulatory loads in the fetus, including the circulation of amniotic fluid, (2) the umbilical cord and placental hemodynamics, (3) the determining mechanism of control of the volume of blood flow through the placenta, (4) the mechanism of closure of the ductus arteriosus, (5) the role of the fetal liver as a blood depot, and finally (6) the homeostatic regulatory mechanisms of fetal heart rate.

*Regional Circulatory Loads in the Fetus.*—The pathways of blood flow in the fetus have been described. Which ones of these carry the greatest and which the least burden? Although we cannot measure the volume flow of blood in them, we may learn much from measurements of its speed in different parts of the circulation.

Careful analysis of x-ray movies of lamb fetuses (weighing from 5 to 12 pounds) provides the basis for our knowledge of this subject. In this work, cinefluorographic pictures were made at a speed of 25 frames per second. Injections of opaque medium in various parts of the circulation made it possible to study the rate of travel throughout the major parts of the vascular tree. The salient points of these experiments may be noted.

It was found that the fetus differs from the adult in a very important way: the speed of circulation through the head is about one-third what it is after birth. Much the same is true of the lungs. In the fetus, a very small quantity



of blood passes into the lungs and it requires about four seconds to pass through them. After ventilation of the lungs has started, however, two seconds or less are required for a very large quantity of blood traveling at a very fast rate to pass through the pulmonary circuit. The most marked difference is in the speed with which the pulmonary arterial tree fills in the fetus and in the breathing animal. In the former, nearly two seconds, or some ten to fourteen ventricular systoles are necessary. In the latter, only a half second, or a single ventricular ejection suffices to fill the pulmonary arterial tree with contrast medium. In short, the flow is slower through some of the main circulatory pathways in the fetus than it is after birth. This is the reciprocal of what is observed with respect to the flow of blood to the caudal part of the organism, especially down the aorta and into the umbilical arteries and so to the placenta. Measurements show that the fastest flow of blood in the fetus is in the lower part of the aorta and the umbilical arteries. Of course, after birth, the latter ceases entirely.

We see, therefore, that in either the fetal or postnatal animal, the fastest and most abundant flow of blood is to the organ of respiration. The circulatory adaptations in each instance are such that this is assured. In the fetus, both ventricles of the heart eject blood into the aorta, mostly into the descending aorta. After birth, the volume of this flow is reduced by about 50 per cent since the blood of the right side of the heart now goes entirely into the lungs as the ductus arteriosus closes.

Another significant change in the pathways of fluid exchange takes place as the fetus becomes newborn. In the uterus, amniotic fluid is formed continuously. There is a 100 per cent turnover of water per hour in the human being near term. One abundant source of this fluid in lambs is from the mucosa of the nasopharyngeal and buccal cavities. There may be as much as 40 c.c. or more formed per hour. By what route amniotic fluid returns to the blood streams of the fetus and the mother is not known. In any case, after birth the circulation of blood to provide for the turnover of amniotic fluid is no longer necessary. The newborn organism differs, accordingly, from the fetus in the small but steady drain on the fluid resources of the fetus which life in utero entails.

*The Umbilical Cord and Placenta.*—A second set of significant facts of importance to our understanding of the hemodynamic character of the fetal circulation relates to the conditions of blood flow in the umbilical cord and placenta.

The size of the job performed in this part of the circulatory system is revealed by the quantity of blood carried through the cord. A human fetus about 14 weeks of age weighs about 2 ounces, yet it "drinks" and discharges by way of the placenta about 6 quarts of water a day. At 31 weeks of age, a 3 pound fetus must move some 70 quarts of water per day. This is dependent upon the fetal circulation, but what adaptations in the character of the cord and placental circulation assure fulfillment of this? The obstetrician knows that umbilical cords vary greatly in length. Cords of 4 to 5 feet in length

have been described. Sometimes, such long cords are wound loosely about the body, extremities, or neck of the fetus. Occasionally they have loose knots tied in them. Clearly, the fetal circulation seems to be independent of the length of the cord or of its twisting and turning. Such knowledge ought to have led us long ago to inquire into the nature of the fetal-placental circulation.

New knowledge concerning blood flow in the cord has come from morphological studies. A cross section of the umbilical cord is generally known to reveal two constricted arteries, a constricted vein, and an abundance of Wharton's jelly. When the cord is clamped simultaneously at two points while blood pulsates through it, a very different picture is seen. The blood vessels are large, thin walled, and distended with much blood, and there is only a small amount of Wharton's jelly stretched in a taut membrane about the three vessels. The structural basis of these differences need not detain us here. It is more to the point to consider what the physiological cause and functional implication of the difference are.

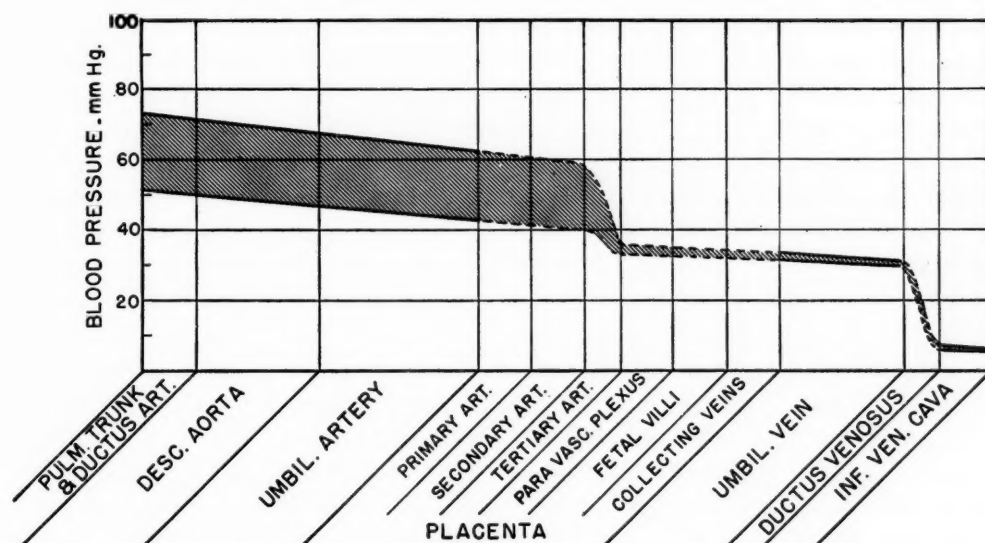


Fig. 1.—Scheme of the blood pressure ranges, observed and hypothetical, in the vascular system of the fetal lamb.

The arteries and veins are distended in life by the pressure of blood within them. In arteries, the pressure is derived from the ventricular ejection into the arteries and resistance peripherally to the outflow of blood into the capillary vascular bed. In the umbilical vein, there is substantial resistance to flow for the umbilical vein pressure is high. In the inferior vena cava, the pressure is low. If pressure were not high in the umbilical vein this structure would collapse. The basis of the resistance to flow has only recently been elucidated.

The umbilical vein has two types of ending in the umbilical recess in the fetal liver. One is the direct connection into the inferior vena cava by way of the ductus venosus. The other is by way of the hepatic circulation into the hepatic veins and thence into the inferior vena cava. A sphincter at the start

of the ductus venosus offers resistance to flow by partial or complete constriction. Otherwise, no blood would pass through the liver circulation, and the umbilical vein pressure would diminish. Normally, in a fetus in late pregnancy the pressure in the umbilical vein is between 30 and 40 mm. of mercury. This is about half the level of arterial blood pressure. In the placenta, the pressure is, of course, intermediate between these extremes.

The fact that the principal site of resistance in this circuit to blood flow is at the end of the vein instead of in the small arterioles of the placenta means that the placental capillary vessels must be under higher pressure than other capillary blood vessels throughout the body.

Another corollary of the high pressure in both the arteries and vein of the umbilical cord is that the pressure serves to keep their lumens large, since a vis a tergo is maintained throughout the system. The umbilical cord is, in a sense, an erectile type of organ. This condition prevents easy obliteration of the lumens of the vessels. By keeping the lumens large, however, there is little frictional loss of energy against the vessel walls, and the main loss is in friction due to viscous flow. It follows, therefore, that the flow along the large, distended vessels of the cord is a function of the difference of pressure between the two ends. With little frictional loss of energy, there may be very copious blood flow even though a small pressure difference exists between the two ends, provided only that the volume of blood available at the supplying end is "infinite," as indeed it is when the fetal circulation is adequate. These unique characteristics combine to assure an ample flow of blood to the placenta, no matter how long or tortuous the cord may be. The sine qua non for this is that the diameters of the vessels remain large, and that the fetal circulation be competent.

*Placental Blood Vessels.*—The nature of the architecture of fetal placental vasculature has presented a paradox until very recently. Obviously it must function as a unit of the umbilical cord circulation with which it is so intimately connected. The well-known Spanner concept of a chandelier arrangement of the minute fetal blood capillary vessels forming an arcade of long capillaries from near the basal chorionic plate coming together into the collecting veins near the subchorial plate presents a difficult concept for the critically minded physiologist. It would create substantial resistance to blood flow.

Recent work by Finn Bøe of Oslo reveals a very different type of placental vasculature. Stated briefly, the arteries of the chorionic and subchorionic plate divide, giving rise to few branches which are of relatively large diameter. There are three such arterial divisions, giving rise to primary, secondary, and tertiary branches. The latter give rise to an extensive paravascular plexus of vessels comprised of numerous short capillary blood vessels and some arteriovenous shunts. From this plexus arise, in any of at least three different forms, small, short vascular units that lie contained in small folds of thin tissue. Such units constitute the fetal chorionic villi. These are as numerous near the subchorial plate as near the basal plate. In location, size, and simplicity, the fetal villus is utterly different from the elaborate unit visualized by Spanner.

What the hemodynamics of these villi is, no one may say with certainty. Arterial pressure would appear to continue at a high level through the secondary arteries, and even, perhaps, to the level of the paravascular plexus (Fig. 1). In the plexus, the small size of the vessels and the extensive size of the vascular tree must slow the rate of flow and decrease the pressure to a level near that in the umbilical vein. There are many arterial branches in the placenta relative to the number of collecting veins. The pressure in the fetal villi should compare with that in the paravascular plexus. Moreover, the large size of the plexus relative to that of the villi should serve to protect the villi from marked or extreme fluctuation in blood pressure by standing as a buffer for them.

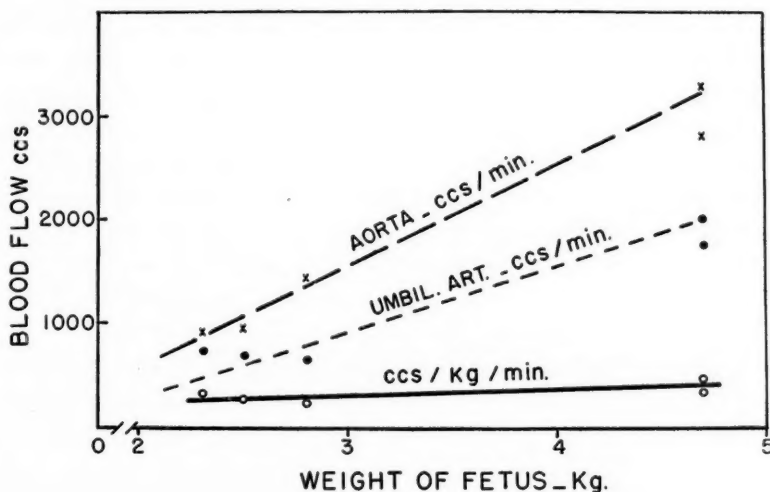


Fig. 2.—Factors affecting blood flow to the placenta in the fetal lamb. Plotted as a function of the weight of the fetus. Note that the flow down the aorta or in the umbilical arteries increases with fetal weight; that the proportion of aortic blood flowing to the placenta is about 66 per cent; and that the flow per kilogram of body weight is about the same at all stages shown.

The umbilical artery-placental vasculature-umbilical vein system stands out as unique within the organism. We see that it is designed in such a way that it permits the fetus to move and change position from time to time. At the same time, the vis a tergo within the system serves to give the umbilical cord certain properties of a rigid tube and to make it a large and capacious structure connecting the fetus and the placenta. Finally, the placental structure is such that the flow, while abundant, is slow through any unit of placental villus tissue. Observations on blood flow through the placenta of the sheep show that the circulation time is about 5 seconds.

What is not accounted for today by any objective observations, or even by any acceptable hypothesis, is the mechanism of transfer of plasma constituents across the placental barrier, between the maternal and fetal bloods. Free diffusion from regions of high to low concentration is part of the mechanism, and active secretion must account for the transfer of some substances. However, the role of hydrostatic pressure over and above the effective osmotic pressure of plasma proteins between fetal and maternal blood, respectively, is unknown



although it is an important factor in capillary fluid transfers in other parts of the body. One pauses to think when he realizes that the pressure within the vessels of the fetal villus is 30 to 40 mm. of mercury, and that in the intervillous space when the uterus is in diastole is less than 10 mm. of mercury. Such a balance should cause a transfer of water from the fetus to the mother.

*Volume Flow of Blood Through the Placenta.*—Everyone accepts the fact that the flow of fetal blood through the placenta is sufficient for fetal growth. No one seems to have asked by what physiological mechanism this is achieved. Is it governed solely by the fetus, or is it modified, especially at the end of pregnancy, by structural limitations imposed by the architecture of the cord and placental blood vessels?

In Fig. 2, the amount of blood flowing from the fetus to the placenta is shown in a graph as a function of the weight of the fetus. This shows that the heavier the fetus, the more blood flows to the placenta per minute. About two-thirds of the blood that passes down the dorsal aorta goes to the placenta. When the volume of blood per kilogram of body weight per minute going to the placenta is calculated, a volume of 300 to 400 c.c. per kilogram per minute is found. This clearly shows that the determining factor in the volume flow of blood is the fetal cardiac output. This, then, is the determining factor of the volume of fetal blood flowing through the placenta. It would seem to be a provident mechanism on the part of Nature to have it so.

*The Sphincter of the Ductus Venosus.*—Mention was made previously of the existence in the beginning of the ductus venosus of a well-defined sphincter. While it is evident that much remains to be learned about this structure, it is clear that certain facts already known attest to its importance for the welfare of the fetus.

The sphincter is known to be innervated by branches of the vagus nerve. By cineangiography, the sphincter has been observed to contract very quickly. It has likewise been observed to open in response to modification in the rate of venous return from the placenta. The view may be tentatively advanced, it seems, that the sphincter of the ductus venosus deflects blood into or away from the fetal liver according to whether or not the sphincter is open or closed. Thus, by directing blood to or away from the liver, it can make the liver act as a temporary reservoir of blood to prevent overloading of the fetal heart. This could occur, for example, when the uterus contracts strongly. At the moment, the evidence for this role is incomplete so this view may be advanced only as a hypothetical one. Even so, the data that do exist on this point indicate that it is the role of the sphincter of the ductus venosus that makes this part of the fetal circulation unique. It is this mechanism, also, which appears to make the fetal circulation so very different from the adult by controlling at this venous station some two-thirds of the total venous return to the heart.

*The Ductus Arteriosus.*—The mechanism of closure of the ductus arteriosus structure has intrigued students of fetal and neonatal physiology for a long time. New data suggest the nature of the mechanism. In this work, cinefluoro-

graphs were taken at a speed of twenty-five frames per second. Blood pressure was measured in the pulmonary trunk and systemic blood pressure in the aorta. In other words, the pressure was measured at each end of the ductus arteriosus. The lamb was delivered by cesarean section, breathing prevented by application of a rubber bag to the nose, and the fetus maintained in excellent condition. The course of blood flow, and the status of the ductus arteriosus were demonstrated by the injection of opaque medium into the appropriate part of the circulatory system. After study of the fetal condition, the observations were repeated upon aeration of the lungs. In this way, blood flow and pressure taken at appropriate intervals of time told the investigators when the ductus arteriosus closed, and what the prevailing pressures in the arterial tree were at the time.

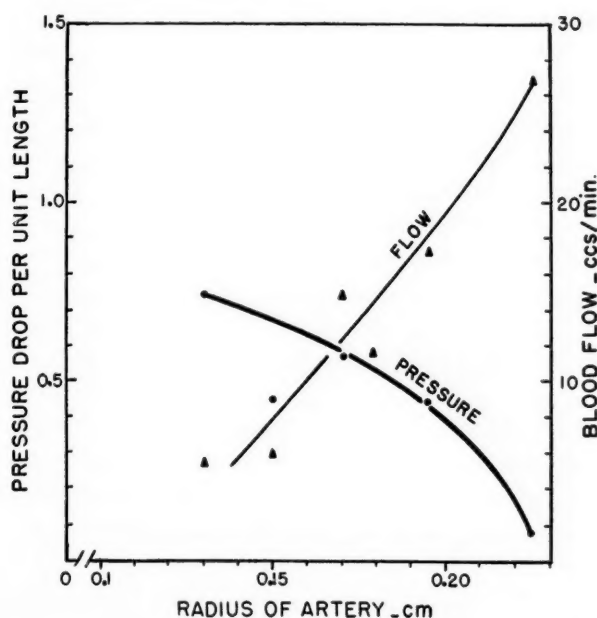


Fig. 3.—Effect of radius of umbilical artery on (a) pressure drop and (b) blood flow.

The results were dramatically clear. Prior to aeration of the lungs the pressure at the beginning of the ductus arteriosus in the pulmonary trunk exceeds that in the aorta, at the other end of the ductus arteriosus. The flow of blood through the lungs is very slow and exceedingly small in amount. Therefore, most of the blood from the right side of the heart enters the aorta through the ductus arteriosus where, in moving pictures of it, one may see the two streams mixing turbulently as the blood rushes along the aorta toward the placenta. This is in the fetal condition.

When ventilation of the lungs is begun, there is a profound fall in blood pressure in both the pulmonary arterial and aortic pressures, just as Schultze predicted in 1871 would be observed. The fall in blood pressure coincides with and depends upon an enormous increase in the velocity and volume of blood flow into the lungs as the minute blood vessels of the lung expand and fill with

blood. The faster flow into the lungs at a lower pressure obviously means that the resistance to blood flow in the lungs diminishes upon aeration of the lungs.

While the blood pours into the lungs, there is a reduction in the return of blood flowing to the heart. This accounts for the reduction in blood pressure throughout the arterial system. Inasmuch as the lungs fill up after a few minutes, blood returns to the heart and so the level of systemic blood pressure recovers. In the pulmonary system, however, the blood pressure remains low. This is because the high resistance to blood flow through the numerous non-expanded blood vessels of the fetal lung becomes very low upon aeration of the lungs. Consequently blood rushes through the lungs and on back to the left auricle of the heart. This change in resistance to blood flow in the fetal lung was measured in 1952 by Dr. G. S. Dawes and his associates, Dr. J. Widdicombe and Dr. Joan Mott of Oxford University.

The changes just described commence with the first filling of the lungs with air, and usually become stabilized within ten to twenty minutes.

What happens to the ductus arteriosus at the time the crucial changes described take place? At what time does it close? Cineradiographs show that it effectively closes within a minute or two of the time of onset of ventilation of the lungs. It closes when the blood pressures in both arterial systems are at their lowest points. Why should this be so?

The answer to this question may be stated today only in hypothetical terms. The best explanation is as follows: Normally, the ductus arteriosus, a distended structure containing elastic and muscular tissues, tries to close at all times, but it is held open by the high blood pressure within it. This results from blood being forced through the ductus arteriosus during fetal life as it is deflected by the high resistance to flow in the lungs. With aeration of the lungs, resistance to blood flow decreases, as previously described, and in consequence blood is diverted from the ductus arteriosus. Then, as the force of blood pressure restraining closure of the ductus arteriosus in the fetus lessens, the ductus arteriosus is able to close. This may be called a hemodynamic theory of closure of the ductus arteriosus.

In support of this view is the fact that when a state of asphyxia is transiently induced when the lamb is in the fetal condition, this is accompanied by a generalized constriction of blood vessels and a rise of blood pressure. Cineradiographs show that the ductus arteriosus closes, too, as the power of its contractile force overcomes the pressure of blood within it. Recently, I have likewise observed this directly in anesthetized fetuses which have opened chests. The ductus arteriosus visibly and powerfully constricts as asphyxia develops.

The concept of ductus arteriosus closure just described is a mechanistic one. It is characterized by simplicity. As such, it stands in contrast to the previous two theories that have been propounded and found wanting. One of these is that the ductus arteriosus closes as the result of nervous reflex action associated with distention of the lungs upon inflation. It has been observed, however, that the ductus closes after the nerves to it have been severed. The innervation is not essential, therefore. The second theory holds that when air fills the lungs,

the oxygen in it acts, when transported by the blood stream, as a stimulus for the muscle of the ductus arteriosus to contract and shut. The fact that the ductus arteriosus closes during asphyxia, when oxygen is low, as just described, belies this. Moreover, physiologists know that oxygen does not act as a stimulant to muscular contraction. The hemodynamic theory recounted previously has the virtue of simplicity, and it fits the known facts.

*Fetal Bradycardia and Reflex Control of the Heart.*—Obstetricians are taught that marked and prolonged slowing of the fetal heartbeat during labor is a sign of fetal distress. Few people have concerned themselves with the physiological basis of this phenomenon, although it has been duplicated by a number of investigators.

Barcroft demonstrated that slowing of the fetal heart is not attributable to simple anoxia. It is abolished in fetal lambs by vagotomy. The reflex, therefore, is associated with a rise in arterial blood pressure when the umbilical cord is clamped. Barcroft reasoned that the reflex is, accordingly, a depressor reflex. Recent experiments show, however, that the same reflex slowing occurs if only the umbilical veins are occluded and there is no increase in blood pressure. On the contrary, there is a fall in pressure with umbilical vein occlusion only as blood moves into the placenta and as venous return to the heart is so largely prevented. The reflex is not modified by excluding the carotid sinus or ablating the stellate ganglia containing the sympathetic nerves of the heart. It is abolished by bilateral vagotomy.

The recovery features from the reflex bradycardia in the fetus reveal other physiological features that have clinical implications. It has been found that when the bradycardia is severe, the heart rate becomes very fast during the period of recovery. This is most marked when the heart is completely denervated (i.e., after double vagotomy and bilateral stellate ganglionectomy), or when the bradycardia is very severe and prolonged. At such times, the heart rate increases to 260 to 280 beats per minute. This is faster than can be counted by auscultation. The tachycardia response during recovery from severe bradycardia depends upon the discharge of endogenous adrenaline inasmuch as it is abolished by bilateral adrenalectomy.

The conclusion follows, from all of these experiments, that fetal bradycardia is a sign of fetal circulatory distress, and if it is followed by an excessively fast heartbeat, the fetus has been and still is in extreme distress. The sympathetic nervous system responds by causing an outpouring of adrenaline into the blood stream.

One other fact of academic interest has come out of recent work. The view is now held that near term, vagal tone develops in the fetus, and this is marked by a slow resting heart rate. Critical evaluation of the situation in new experiments in fetal lambs suggests, however, that there is no appreciable vagal tone in the fetus at rest before birth. However, the slightest degree of fetal circulatory distress induces demonstrable vagal tone. Similarly, there is no evidence of carotid sinus or sympathetic tone in the fetus, although activity over all these reflex pathways may be initiated by adequate stimulation.



It appears that the lamb fetus in utero is normally protected from stressful situations so that the reflex mechanisms of cardiac control do not function, even though they are demonstrably capable of it. An essential element of vagotonia is that the organism must be exposed to frequent or continuing conditions of stress in the external environment. The fetus in utero is relatively free from such stresses. In adult animals, such as dogs and human beings, inactivity and lack of the stress of training lead to a loss of physiological conditioning. This includes reduced vagal tone. Just so, the fetus fails to exhibit those attributes which are associated with physiological conditioning. For this reason, no doubt, the fetus in utero appears to react "paradoxically" to circulatory stress, for the cardiovascular system is operating at rest without benefit of measurable vasomotor tone comparable to that of postnatal animals. One should not expect, therefore, that the responses of such a system will duplicate those of the adult who has cardiac autonomic tone. Such an explanation accords with the observations made in the lamb fetus and it is consonant with the generally accepted knowledge of the development of vagal and sympathetic tone in postnatal animals.

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## HYPOXIA IN FETAL AND NEONATAL LIFE

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LIVING organisms consume energy and this comes from the degradation of complex organic materials. This degradation is accompanied by the formation of simple compounds and the liberation of free energy. The degradation is either oxidative or nonoxidative, that is aerobic or anaerobic. Till recently it was thought that measurable energy supplies came only from carbohydrates, fats, and proteins and that the last group had a dynamic action of such magnitude that their metabolism involved a consumption of energy greater than that liberated by their degradation, this extra energy consumed coming from the degradation of other sources of energy, notably carbohydrate and fat. In recent years it has come to be appreciated that the ruminant obtains much of its energy supplies from fatty acids produced in the rumen by the fermentation of cellulose and other sources. Further, it has been appreciated that these fatty acids can be utilized by other animals besides ruminants.

Aerobiosis and anaerobiosis have been long recognized as being differences of metabolism by which microorganisms could be classified. Potential anaerobiosis is present in all mammalian tissues between termination of oxygen supply and death of the tissue and organism. In fact, as we know from the studies of metabolism of adult muscles and nerves from the time of Fletcher and Hopkins (1907) to the present day, the actual liberation of energy with which the contraction of the muscle can take place is anaerobic. The oxygen is needed for its replenishment within the muscle from oxidative sources of energy. There is, therefore, the question both of the immediate energy source and of the replenishment source for energy and the mechanism involved.

These two problems have also presented themselves in two other forms, namely, the comparative problem and the differential tissue problem. The former concerns the mechanism by which different species solve these two questions of immediate and replenishment sources of energy. The latter concerns the evidence for different maturation rates in different tissues and for different sources for both the immediate and replenishment energy supplies.

### *Anoxic Survival.—*

The concept of the fetus or newborn surviving undue periods of time in the absence of oxygen first arose out of the work of Reiss and Haurowitz (1929) who showed that young mice or rats were vastly more resistant to anoxia than adults. This, Reiss (1931) showed, was associated with excep-

tional ability to form lactic acid. Wilson and his colleagues (1937) demonstrated that asphyxia adequate to kill an adult leaves the human infant still responsive to lobeline. Kabat (1940), producing cerebral anemia in dogs, found the respiratory mechanism functioned in puppies seventeen times as long as in adult animals. This he correlated with Craigie's (1925) findings that the vascularity of the brain in the rat increases over 400 times between birth and adulthood. Simultaneously in 1941 Selle and Witten decapitated young rats and found the decapitated head gasped apparently in two series, the earlier aerobic series being somewhat separated from the later anaerobic series. Thoms and Hiestand (1947) showed the first series lasts throughout life but the second series progressively lessens and disappears about the nineteenth day after birth.

It would, therefore, appear that, by the end of the peace between World Wars I and II, evidence had been assembled that in animals and man hypoxia in one form or another in the newborn or fetus or the premature does not necessarily mean cessation of nervous, respiratory, cardiac, or muscular activities and that they persist under conditions which would be fatal in adult animals.

It is proposed to consider some physiological conditions of the fetus or newborn in which low oxygen tensions may or may not play a part and to evaluate in some degree the role of hypoxia in early life of the mammalian organism.

### **The Onset of Pulmonary Ventilation**

The physiological mechanisms controlling the onset of external respiration are not well understood, and up to the present time there seem to be only two hopeful lines of investigation. The first is to examine any respiratory movements which occur either in utero or in a warm saline bath with an intact circulation through the umbilical cord. The second method is to examine the control of respiration once air breathing has been established. At both these stages it is possible to undertake a considerable amount of experimental interference, and to extend the times of observation of the intrauterine stage quite close to the extrauterine stage, but at the moment it has to be appreciated that there are essential differences between these two stages and we are examining a continuous yet slowly changing system. In considering the onset of respiration one can examine established knowledge in the two phases and mention the possible pointers toward investigation of the mechanism of the time of change-over.

#### *Fetal Respiratory Movements.—*

Huggett (1930) and Barcroft (1946) have shown that the fetus has a developing system of reflex respiratory responses to stimuli which in some ways parallel the more obvious morphological developments. It is interesting to note, however, that the vigor of respiratory movements under normal conditions diminishes as term is approached, although it is probable that slight tidal movements of amniotic fluid continue. The fetus differs strikingly from the adult, however, in response to carbon dioxide and oxygen. While the

adult shows the most marked changes to increases of partial pressure of carbon dioxide, the fetus, observed in the saline bath, seems not to respond so markedly to large doses administered to the mother. The reverse is true in the case of low oxygen, which will both stimulate the mother's breathing and also cause severe gasping movements in the fetus. This sensitivity to oxygen lack would appear to be true of the fetus which is still genuinely in utero, for conditions which give rise to fetal anoxia, such as faulty induction of anesthesia in the mother, detached placenta, prolapsed cord, or delayed delivery of the aftercoming head, all frequently result in marked intrauterine respiration. If there is a "marker substance" present in the amniotic fluid in the form of meconium, this is often found at postmortem on the stillborn infant to be in the lung alveoli. In the sheep fetus at 140 days it has been shown that the chemoceptor nerves are carrying impulses when the mother is being artificially ventilated on air and is under chloralose anesthesia. These impulses increase markedly if the mother is ventilated on a low oxygen mixture (Cross and Malcolm, 1952). This approach does not, of course, measure the response of the medulla to this chemoceptor bombardment and Barcroft and Karvonen (1948) have produced evidence to suggest that the total chemoceptor reflex is diminished as term approaches. In summary, it appears that the fetus near term has stimuli present which might well cause vigorous respiratory activity, but this is inhibited while pregnancy remains physiological.

*Respiration of the Newborn.—*

If one examines the already established respiratory behavior of the newborn infant we find that there are striking differences when it is compared with both that of the fetus and of the adult. The most obvious difference is the respiratory irregularity which appears to mimic fetal rather than adult behavior. When the newborn infant receives carbon dioxide in the inspired air there is a marked respiratory response which is relatively greater than that of the adult (Cross, Hooper, and Oppé, 1953) and is strikingly different from that of the fetus, who does not respond to the same extent when the maternal arterial partial pressure of carbon dioxide is raised. The response of the newborn infant to lowered oxygen is somewhat more complicated. When he is breathing 15 per cent oxygen there is an increase in the minute volume of respiration but, unlike the condition in the adult, the efficacy of the stimulus is very short lived and the respiratory minute volume rapidly declines to normal levels. When air is again given there is a further marked drop in the minute volume of respiration and this has been interpreted to indicate that the peripheral chemoceptor areas are persistently stimulated by low oxygen but the infantile respiratory center is rapidly depressed, causing the minute volume to diminish. The administration of the air removed the peripheral stimulus and the depressed center, receiving fewer peripheral stimuli, responded still less (Cross and Oppé, 1952) (Cross, Hooper, and Lord, 1953). This depression of the respiratory center has recently been confirmed by comparing the effect of a small dose of carbon dioxide in air with the same dose of carbon dioxide in a low oxygen mixture. It is found that if the infant had previously been made hypoxic then the response to carbon dioxide was grossly dimin-



ished. If one now evaluates and compares the total respiratory response of the infant to low oxygen with that of the fetus and the adult, the situation is not so clear-cut as with carbon dioxide. There seems to be no doubt that the adult medulla is depressed by anoxia only when the oxygen lack becomes extreme (less than 5 per cent carbon dioxide in the inspired air), while the infant soon shows medullary depression with 15 per cent oxygen. There is no doubt that in the fetus the partial pressure of oxygen in the umbilical vein blood is falling during the latter part of pregnancy and therefore the medulla must be suffering from some degree of oxygen lack under normal conditions. By analogy with the infant one might expect this to depress respiratory activity, but it appears uncertain that medullary depression is extreme for, as has already been mentioned, if acute anoxia is added to the chronic anoxia, then marked respiratory stimulation is produced. This must be the result of chemoreceptor bombardment of the medulla if the current picture of respiratory control is at all well understood.

*Effect of Delivery.—*

At birth there are three major changes which may well influence the onset of respiration. These may be divided into (1) new sensory stimuli, (2) vascular changes, and (3) an increase of hypoxia.

1. The sensory stimuli are certainly profoundly efficacious in producing breathing in many babies and may well change the central excitatory state of the nervous system.

2. The vascular changes are chiefly concerned with an increase in blood flow through the pulmonary arteries and a fall in umbilical pressure. Dawes and associates (1953) have shown that the increase of pulmonary vascular flow appears to follow the ventilation of the lungs with a gas mixture, rather than the reverse, so possible reflexes from the pulmonary vascular bed cannot be invoked to explain the onset of respiration. Another striking vascular change, which has received less attention, is the marked fall in umbilical vein pressure which occurs when the cord is tied or the umbilical circulation diminishes. This fall in pressure generally precedes the onset of respiration and it is attractive to imagine that some inhibitor mechanism which is preventing the fetus from breathing is lost when this pressure falls. This speculation is made more attractive by the work of Reeve and co-workers (1951), who have shown that in the adult there are several areas in the abdomen which inhibit respiration on stimulation and the most active of these areas appears to be the ligamentum teres. Unfortunately, for such a hypothesis, it is well known that the umbilical cord contains no nerves and examination of the intra-abdominal course of the umbilical vein has failed to reveal nerve endings suitable for such a reflex.

3. The third stimulus of increasing hypoxia is present at birth and it is of interest to note that in the ordinary life of the ordinary mammal late pregnancy and birth are the only occasions when hypoxia will certainly be experienced. It seems most probable, from present knowledge, that the stimulus of oxygen lack is responsible for the onset of respiration. It should be

recognized that it has to be explained why the progressive hypoxia of late prenatal life does not cause more marked intrauterine breathing and also how it is that a medulla, which is easily depressed by low oxygen in immediate postnatal life, can be stimulated by a further fall in oxygen tension when the emergency of birth occurs.

### **Fetal Hemoglobin and Oxygen Transport**

It is well known that in most mammals the hemoglobin found in the blood of the fetus differs in many respects from that found in the blood of adult animals of the same species.

Chemically the differences can be discerned in the globin part of the molecule; there are small differences in the proportions of the various amino acids, but the main physiological characteristic, namely the oxygen-binding capacity, remains unaltered: 1 Gm. of hemoglobin whether from fetal or adult animal combines with 1.34 ml. of oxygen. The molecular weight of each form of hemoglobin has been established as 67,000. Use has been made of various physicochemical properties of hemoglobin in distinguishing between the fetal and adult forms. For example (Brinkman and Jonxis, 1935), human fetal hemoglobin spreads much more slowly to form a monomolecular layer on the surface of a buffer solution at a pH near the isoelectric point than does adult human hemoglobin. It is more slowly denatured in alkaline buffer solution (pH 12.7) (Brinkman, Wildschut, and Wittermans, 1934) and it is less readily soluble (Joep and O'Brien, 1949). It is a curious fact that these relationships are exactly reversed in the case of the goat, sheep, and cow. In all these species the fetal form of hemoglobin is more soluble (Wyman, Rafferty, and Ingalls, 1944), more rapidly denatured in alkaline solution (Brinkman and Jonxis, 1936) and spreads more rapidly at the isoelectric point than the respective adult form. Whether these chemical characteristics have a functional significance it is impossible to say.

Clearly the behavior of hemoglobin in taking up oxygen is of considerable functional significance and here too the various hemoglobins exhibit small differences.

A curve describing the degree of oxygenation of the hemoglobin at varying partial pressures of oxygen (the oxygen dissociation curve) and at constant pH, temperature, and partial pressure of carbon dioxide defines the physiological properties of hemoglobin. If hemoglobin is dissolved in a buffer solution the fetal form has a curve that differs from the adult one (Hall, 1934). Again the human fetal hemoglobin behaves somewhat differently from that of the cow (Roos and Romijn, 1941), sheep, or goat. In these species the fetal hemoglobin has an oxygen dissociation curve displaced to the left of that for the corresponding adult hemoglobin, whether the measurements be made on solutions of hemoglobin or on whole blood. Hemoglobin from the human fetus exhibits an oxygen dissociation curve which lies a little to the left of the average curve for adult hemoglobin, but if whole blood from the human fetus be compared with whole blood from the mother (Eastman, Geiling, and De Lawder, 1933) the difference between them is accentuated, the curve for ma-

ternal blood lying slightly to the right of the average (Leibson, Likhnitzky, and Sax, 1936; Darling, Smith, Asmussen, and Cohen, 1941). When McCarthy (1943) investigated the point further he obtained the curious result that the maternal hemoglobin when liberated from the cells behaved differently, exhibiting a dissociation curve shifted to the left. This finding does not seem to have been satisfactorily explained, but perhaps it need not concern us too much, since it is the behavior of the hemoglobin within the cells that is of physiological importance. All investigators are agreed that when fetal blood is compared with maternal blood the former has a higher affinity for oxygen than the latter. This fact must be considered in the light of our knowledge of conditions in the placenta. The maternal arterial blood may be assumed to be saturated to about 97 per cent of its capacity with oxygen and to carry dissolved oxygen at a tension of 85-85 mm. Hg in equilibrium with the hemoglobin. This blood probably leaves the placenta, in the later months of pregnancy, with its hemoglobin not much more than half saturated with oxygen.

Measurements of the oxygen content and capacity of the fetal blood at or slightly before full term (Eastman and collaborators, 1933) have shown something of the order of 30 per cent saturation in the umbilical artery and 60 to 65 per cent saturation in the umbilical vein. Walker and Turnbull (1953) have found somewhat lower values. It would be impossible by simple diffusion for the blood in the umbilical vein to reach an oxygen saturation higher than that of the maternal blood leaving the placenta, if it were not for the differing oxygen affinities of these two bloods. If we consider the pressure gradient available to regulate the diffusion of oxygen the advantage gained by the differing oxygen affinities becomes very evident.

Maternal blood enters the placenta carrying oxygen at a tension of, say, 90 mm. Hg; if it loses 40 per cent of its oxygen in passage through the placenta it will emerge with an oxygen tension of approximately 30 mm. Hg. The mean capillary oxygen tension of the maternal blood in the placenta must be somewhere between these extremes, possibly 50 mm. Hg or less. Fetal blood reaches the placenta near to full term carrying oxygen at a tension of approximately 15 mm. Hg. and leaves it at a tension of about 27 mm. Hg. These are all approximate values, but it appears from them that complete equilibrium is approached with respect to oxygen tension between the maternal and fetal blood in the placenta. Under these conditions the maternal blood would leave the placenta about 55 per cent saturated while the blood in the umbilical vein would be 65 per cent saturated.

The other side of the picture is the unloading of oxygen in the fetal tissues. It is clear that the tissue oxygen tension must be low; if we consider the limit set by the tension in the umbilical artery it would be less than 15 mm. Hg. The umbilical artery of course contains mixed venous blood, some of which has flowed through two sets of capillaries, so it is possible that some tissues have an oxygen tension somewhat higher than this. Nevertheless, it seems clear that fetal tissue metabolism must be carried on at a tension of oxygen considerably lower than that which obtains in postnatal life. One

factor or possible importance has not been considered and that is the production and carriage of carbon dioxide. The few measurements of carbon dioxide (Eastman and associates, 1933) content and tension in the umbilical arterial and venous bloods suggest that neither of these values departs greatly from those in adult arterial and mixed venous blood. We know so little of the conditions in fetal capillaries and tissues, however, that it would be unwise to conclude that variations in pH or in carbon dioxide tension or in both do not affect the "unloading tension" of oxygen in the tissues. Another interesting problem about which we know little concerns the regulation of the synthesis of hemoglobin, and the factors that determine the exact nature of the globin part of the molecule. Two tempting hypotheses suggest themselves: one, that the hemopoietic sites characteristic of fetal blood formation synthesize the fetal form of hemoglobin while the bone marrow synthesizes the adult form; the other, that the hypoxic condition of the fetus induces an adaptation in the process of synthesis or of red-cell formation resulting in an altered affinity for oxygen. Unfortunately, such evidence as is available fails to support either hypothesis. Jonxis (1949) compared the proportion of fetal to adult hemoglobin in the liver and in the bone marrow of newborn infants, but could not find any difference between them. On the other hand, there is no evidence that hypoxia in the adult induces any adaptive changes in the hemoglobin although other changes occur in the process of acclimatization. Whether hypoxia induced experimentally after birth would extend the time during which fetal hemoglobin persists is not yet established.

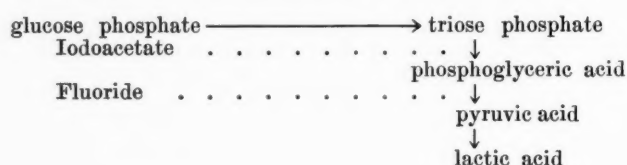
### Experimental Anoxia

It has been mentioned previously that Wilson and his colleagues (1937) found that asphyxia that would kill an adult leaves the human newborn infant with a respiratory center responsive to lobeline and that Reiss (1931) had found that young rats had a greater ability than adult rats to form lactic acid from carbohydrate, suggesting that this might account for their increased survival rate. R  ih   (1941) demonstrated that newborn infants—premature and full term—excrete high amounts of pyruvic and lactic acids but that after the first twenty-four hours from birth the pyruvic acid which was the highest dropped off but lactic acid continued.

Himwich and his colleagues have investigated the whole question of survival in anoxia. With Fazekas (1941) he has shown that the oxygen consumption of newborn brain is less than that of adults. Further, respiration lasts longer in the newborn rat than in adults, when subjected to anoxia. In puppies all arterial oxygen had gone in 5 minutes but respiration went on for 24 minutes and the electrocardiogram for 35 minutes (Himwich, Alexander, and Fazekas, 1941). They have also shown that the tolerance to anoxia decreases with age in any one species and from species to species with the age from conception. Guinea pigs were least tolerant (gestation period 60 days) and rat most tolerant (gestation age 21 days) (Fazekas, Alexander, and Himwich, 1941).



Himwich now put forward the proposition that if anaerobic glycolysis is proceeding with the liberation of energy, its path will be



and that this pathway can be interrupted by iodoacetate and fluoride at the points shown, namely, iodoacetate stops formation of phosphoglyceric acid and fluoride allows this but stops formation of pyruvic acid. With Birnstein, Herrlich, Chesler, and Fazekas (1942) he found that this was so. These two enzyme inhibitors diminished survival time in nitrogen from 20 minutes to 2½ and 7 minutes, respectively. Cyanide on the other hand knocks out the cytochromes, the iron-containing oxidase enzymes of the tissues. Cyanide, he found, reduced a ratling in oxygen to a survival time equal to that of life in nitrogen (Himwich, Alexander, and Fazekas, 1941). He now found that insulin given to adult and to infant rats yielded hypoglycemia in both but the adults became comatose and died whereas the infant rats survived 5 to 10 hours. If, however, the rat was in nitrogen when the insulin was given, then the survival time in nitrogen was reduced from 50 to 25 min. The survival time in nitrogen could be prolonged by means of glucose even if no insulin were given.

In addition to these experiments of Himwich and his colleagues it is necessary to bear in mind that the newborn infant exhibits an acidotic state with increased pyruvic and lactate acids in the blood (Wilson, Reardon, Murayama, 1948).

### Conclusions

It is clear, therefore, that the newborn young animal or human being have in common certain characteristics. These are also present in an accentuated degree in the premature, namely, acidosis or borderline acidosis (Branning 1942), abnormal amounts of fixed acids (not ketone bodies), notably lactic and pyruvic. It also possesses the power to exist without oxygen for prolonged periods which ability is diminished if the blood sugar is lowered by insulin and increased if glucose is administered. A mechanism by which the anaerobic energy supplies in hypoxia is achieved has been proposed by Himwich. The ability to utilize glucose anaerobically is of interest when it is remembered that growing animals in utero have more than one type of carbohydrate available. All fetuses have glucose in their blood. In ruminants (Bacon and Bell, 1948), however, this is of less quantity than the fructose present in the blood. In human fetuses Hagermann and Villee (1952) have found traces of fructose up to 4 to 5 mg. per cent but glucose is the main sugar of the blood. In the rodent and the human being, however, there is glycogen in the placenta. Villee (1953) has shown that the human placental glycogen can form glucose in vitro.

All fetal tissues can utilize fructose aerobically but only a few can utilize it anaerobically. These include the placentas of the cat, ferret, and man (Dickens and Greville, 1932).

A further point to be borne in mind is the fact that growing animals can store carbohydrates and amino acids under the influence of growth hormone of the anterior pituitary body, and which action occurs depends on whether the animal is growing or not (Young, 1953).

It appears, therefore, that there is considerable evidence that newborn and premature animals, including human beings, possess a power of potential anaerobiosis which is lost in the adult. This anaerobiosis appears to depend upon glycolysis and can act as a reserve of energy.

In two mechanisms which occur in the body at and before birth, namely, the formation of hemoglobin and the respiratory ventilation of the newborn (whether full term or premature), there is evidence that hypoxia plays an important part. At the low oxygen tension of the fetal blood there is evidence that the transfer is accomplished and a relatively high saturation achieved by reason of the special properties of fetal hemoglobin. At the same time Walker and Turnbull (1953), by their measurements of the red cell, hemoglobin, and oxygen contents and saturations of the human cord blood between the tenth week (menstrual age) and full term, form the opinion that not only is there a hypoxia but also that while normal adult hemoglobin levels (14.3 Gm.) are reached at the twenty-third week, exceptional hypoxia easily eventuates and this forces the hemoglobin and red-cell levels to exceptionally high values. This occurs with prolongation of labor beyond full term or in pre-eclampsia. In the respiratory mechanism the quiescence of respiratory movements in utero is dependent upon hypoxia depressing the medulla. On the other hand, at birth hypoxia appears to be, in the presence of other factors, one which precipitates respiration, a reversal of its role not yet clearly understood. There is evidence too that in the tissues the intracellular metabolism is geared to a hypoxia which results in an acidosis but which confers considerable reserves of activity upon the cells, enabling them to function at low oxygen tension. This power of action is lost in the adult and in fact disappears fairly early in neonatal life. One catabolic mechanism on which it depends is the glycolytic breakdown of glucose.

It appears that hypoxia is not an incidental factor but a necessity of fetal life and an important influence in neonatal life.

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## OBSTETRICAL FACTORS IN THE ETIOLOGY OF CEREBRAL PALSY\*

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IT IS the purpose of this paper to present an analysis of the antepartal, partal, and neonatal records of 61 obstetrical cases in which the infants, all born at the Johns Hopkins Hospital, subsequently developed the syndrome of cerebral palsy. The number of cases surveyed is avowedly small but this report is believed to be justified nevertheless on the grounds that our records contain detailed data on many of the vagaries of pregnancy, labor, and the neonatal period which have not hitherto been studied in relation to the etiology of cerebral palsy.

These 61 cases were culled from the records of the Maryland League for Crippled Children and the Harriet Lane Home for Invalid Children of the Johns Hopkins Hospital. In initiating this study it was our desire to compile as large a list as possible of cases of cerebral palsy in which the child had been born on our delivery floor, and then to go back and review in detail the antepartal and labor data on these cases. This would seem to be a fairly simple undertaking, but it was made surprisingly difficult by the fact that the cerebral palsy case records available to us rarely mentioned the name of the hospital in which the infant had been born. Since the Johns Hopkins Hospital delivers only about 7 per cent of the infants born in Maryland, our problem was to search for and identify the one case in fifteen of cerebral palsy in which delivery had occurred in our institution. This was finally accomplished to the extent of 61 cases (1) by concentrating on patients who were currently under active diagnostic or therapeutic surveillance in Baltimore, because in these cases the parents could be asked directly where the child had been born, and (2) by checking all the cases seen in the Harriet Lane Home of the Johns Hopkins Hospital because it was reasonable to suppose that a substantial proportion of these children had been born in the same hospital.

The difficulties encountered in collecting these cases have been stressed because: (1) They account for the paucity of cases in this report. (2) They explain the preponderance of recent cases here analyzed because patients under active clinic supervision in Baltimore were for the most part 2 to 8 years old. (3) The omission in the cerebral palsy records of the name of the hospital in which births had occurred is a lapse not limited to Maryland but one which

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has been mentioned by authors elsewhere who have undertaken similar studies. It may be mentioned in passing that the obstetrical records of most hospitals reveal even greater inadequacies for the purposes we have here in mind.

As shown in Table I, and for the reasons just mentioned, 33, or slightly over half of the patients available for study, were born between 1945 and 1949. Since 11,195 surviving infants were born in our hospital during these five years (hereafter called the control series), the number of cases of cerebral palsy which we were able to locate was 2.9 per thousand infants who survived and left the hospital alive. However, in view of the "hit and miss" method we used in unearthing these cases, there is reason to suspect that as many cases were missed as were located; and that, by the same token, our figure of 2.9 per thousand is altogether in keeping with the incidence reported by Levin, Brightman, and Burt from Schenectady County, New York, namely, 5.9 cases of cerebral palsy per 1,000 infants born and surviving one month. The figures for the three five-year periods before 1945 represent merely cases seen at the Harriet Lane Home of our hospital and constitute obviously only a small fraction of the total instances of cerebral palsy which developed in those periods among infants born in our hospital.

TABLE I. DISTRIBUTION OF 61 CASES OF CEREBRAL PALSY BY YEAR OF BIRTH AND BY INCIDENCE OF PREMATURE BIRTH (UNDER 2,500 GRAMS)

YEAR OF BIRTH	PREMATURE	FULL-TERM	TOTAL
1930-1934	2	2	4
1935-1939	4	3	7
1940-1944	5	7	12
1945-1949	6	27	33
1950-1951	1	4	5
Total cases	18	43	61

As is true in other reports, the incidence of premature births in this series is very high, namely, 30 per cent. In the control series of 11,195 births in our hospital with surviving infants mentioned previously, the incidence of premature birth was 9.2 per cent, or less than one-third of the frequency met in the cerebral palsy group. The question here is why premature birth predisposes to the development of cerebral palsy since the fact itself seems to be well established. Is it the underdeveloped state of the infants per se which is to be incriminated, or is it rather certain obstetrical complications which in turn cause both intrauterine anoxia and premature birth? We shall return to this question when we come to discuss the incidence of repeated and prolonged uterine bleeding in this series of pregnancies. Table II shows the type of neurological disorder manifested in the 61 cases as established by specialists in the field. It will be noted that the incidence of premature births was about the same in the several types. As our investigation proceeded, this same observation was found to obtain in respect to other possible etiological factors.

The mean age of the 61 mothers of these infants at the time of birth was 25.4 years. In our control series of 11,195 births with survival of the infant during the period 1945-1949 (when most of the cerebral palsy infants were

born), the mean age was 25.8 years. In other words, in this particular cerebral palsy series the average age of the mother at the birth of the child was almost identical with the average age of comparable patients in the clinic population as a whole. The distribution of white and nonwhite patients in the series, 29 and 32, respectively, is approximately that of the control series. Likewise, the parity of the mothers, their pelvic measurements, and their serologic tests for syphilis showed nothing of significance. The incidence of Rh negativity in the mother was approximately that in the control series, and only one mother showed isoimmunization. None of the 61 infants showed jaundice during the first 48 hours of life. Hence, our series, like others, provides no evidence to suggest that isoimmunization to the Rh factor is a common cause of cerebral palsy.

TABLE II. DISTRIBUTION OF 61 CASES OF CEREBRAL PALSY BY NEUROLOGICAL TYPE

TYPE	PREMATURE	FULL-TERM	TOTAL
Spastics	15	39	54
Diplegia	4	19	23
Hemiplegia	3	10	13
Paraplegia	5	6	11
Double hemiplegia	3	4	7
Flaccid	1	3	4
Rigid	1	1	2
Ataxic	1		1

Table III shows the frequency with which vaginal bleeding was reported in the course of these 61 pregnancies. Bleeding some time in the course of gestation and prior to the onset of labor was reported in 24 cases, or 39.3 per cent. This figure is very high, and, depending upon one's definition of bleeding and the particular control series used, is at least twice, probably three times, the frequency with which bleeding is ordinarily encountered in pregnancies which continue to viability. Of the 24 mothers who experienced bleeding at some time in the course of pregnancy, 5 bled both before and after the twentieth week. In other words, approximately one-fifth of these mothers who bled experienced repeated attacks of bleeding both in the first and second halves of pregnancy. One patient bled daily from the fourteenth to the twenty-first week, and another off and on throughout the entirety of gestation. Even more noteworthy is the incidence of bleeding in those pregnancies which terminated prematurely. In these 18 gestations which terminated prematurely, vaginal bleeding at some time in the course of gestation was reported in 12, or two-thirds. Moreover, in 9 of these 12 cases, bleeding occurred both in the first and second halves of gestation.

TABLE III. INCIDENCE OF VAGINAL BLEEDING IN 61 PREGNANCIES IN WHICH THE INFANT SUBSEQUENTLY DEVELOPED CEREBRAL PALSY (18 INFANTS WERE PREMATURE AND 43 FULL TERM)

STAGE OF PREGNANCY	PREMATURE	FULL-TERM	TOTAL
Sometime during pregnancy	12	12	24
Before the twentieth week, only	3	6	9
After the twentieth week, only	5	5	10
Before and after the twentieth week	4	1	5

By whatever standard one chooses to apply, the frequency of vaginal bleeding in this series, especially repeated vaginal bleeding leading to premature birth, is extraordinarily high. Indeed, in the premature group, the pregnancies seemed to follow a rather definite pattern, namely, repeated episodes of bleeding, until the process of bleeding itself finally initiated premature labor. There were 4 cases of outright abruptio placentae in the series, all occurring before maturity of the fetus. This is many times the expected incidence.

Bleeding in pregnancy means as a rule only one thing and that is placental separation of a greater or lesser degree. In turn, placental separation, according to its degree, must necessarily mean some encroachment on the oxygen supply of the fetus and when more than one-third of the placenta is detached fetal death from anoxia usually ensues. Quite obviously, the degree of placental detachment which occurred in the present series was sublethal in degree, but the vacillating levels of hypoxia which sublethal placental detachment must impose on the fetus can easily be pictured, as can also the effect which the associated shifts in fetal oxygenation, especially if repetitive, would exert on immature neural tissue.

The high frequency of bleeding in the 61 pregnancies was the only conspicuous prenatal finding, since the incidence of toxemia, hyperemesis, anemia, diabetes, intercurrent infection, including virus infections, and of other prenatal complications was not greater than in the clinic population at large.

In regard to labor the average duration in these 61 cases showed little deviation from the normal, but there was a high percentage of prolonged second stages in the full-term group, namely, 12 per cent over three hours. This is roughly four times the usual frequency with which such prolonged second stages are met. Forceps rotation of the head extraction because of prolongation of the second stage, plus posterior position of the occiput, was performed in 5 cases, which is nine times the usual incidence of this particular operation in our clinic. These two observations, the increased frequency of prolonged second stages, and of forceps rotation of the head are suggestive; but the number of cases concerned is extremely small, and, moreover, even if the same finding could be documented in a larger series, it would be difficult to say whether fetal anoxia, so common in the second stage, the trauma of the forceps procedure, or a combination of the two, were to be incriminated. Although a disproportionately high percentage of our so-called "spontaneous deliveries" in this series were accompanied by vigorous abdominal pressure or traction on the head because of shoulder difficulty, trauma in the course of delivery did not appear to be a conspicuous feature of these cases. Contrariwise, labor was so rapid and ostensibly so easy in 6 cases, or 10 per cent, that the baby was born in the patient's bed without the presence of any attendant whatsoever. This figure is very high for unattended deliveries in our clinic and suggests that very rapid labor during which tempestuous and unremitting uterine contractions impose both anoxia and trauma on the fetus is a more important cause of brain injury than prolonged labors or forceps operations in competent hands.

Aside from the frequency of bleeding in pregnancy the most outstanding finding in this study was the poor condition of the infants at birth and in the neonatal period (Table IV). Careful records are kept on all babies in regard to the precise time of the first breath (breathing time in seconds), as to the precise time of the first clearly audible cry (crying time in seconds), the presence and degree of cyanosis, the presence and degree of flaccidity, and finally as to the use of resuscitative measures, such as positive pressure and medicinal stimulants. On the basis of these several criteria, no less than 33, or one-half, of these infants were stated to be in "poor" condition at birth. Infants whose condition at birth is stated to be "poor" in our clinic constitute a rather small group, less than 5 per cent. Moreover, the majority of infants who are so classified die within the first few days of life, the survival rate of infants in this category being low. The fact that over 54 per cent of cerebral palsy cases fell into this category is significant despite the small size of the series.

TABLE IV. CONDITION AT BIRTH OF 61 INFANTS WHO LATER DEVELOPED CEREBRAL PALSY

CONDITION AT BIRTH	PREMATURE	FULL-TERM	TOTAL
Poor (with or without cyanosis)	10	23	33
Good	8	20	28
<i>Breathing Time.</i> —			
0-59 seconds	7	22	29
60 seconds or more	1	14	15
Unknown	10	7	17
<i>Crying Time.</i> —			
0-59 seconds	7	16	23
60 seconds or more	0	12	12
Unknown	11	15	26

TABLE V. HOSPITAL STAY OF 43 FULL-TERM BABIES WHO LATER DEVELOPED CEREBRAL PALSY

DAYS IN HOSPITAL	INFANTS
0-5 days	6
6-10 days	13
11-15 days	10
16-20 days	7
21-25 days	2
26-30 days	0
31-35 days	1
36-40 days	1
41-45 days	1
46-50 days	1
51-60 days	1

Further evidence that these were gravely handicapped babies is shown by the duration of hospital stay of the 43 mature infants as shown in Table V. The hospital stay of premature babies depends chiefly on the degree of prematurity and is not necessarily an index of their state of well-being over the neonatal period. On the other hand, the average stay of mature babies in our clinic, as shown by the control series, is 5.3 days and, with rare exceptions, any appreciable prolongation in the stay of mature babies is indicative of difficulties of one kind or another. The average stay of the 43 mature babies in this series was 14.9 days. Recalling again that the average stay of a mature baby



in our nurseries is 5.3 days, 37 of the 43 mature babies in this series, or 86 per cent, were kept for six days or more. The pediatric notes indicate that the main reasons for the prolonged hospitalization were respiratory irregularities, attacks of cyanosis, feeble cry, inability to nurse, feeding difficulties, and failure to gain in weight. Only 3 infants had convulsions. When the infants finally left the hospital, the pediatric discharge note included a guarded prognosis in 21 cases, or approximately in one-half.

In this small series, accordingly, the poor condition of half the babies at birth, their prolonged hospital stay, and their pathological behavior during the early neonatal period were very striking findings. Provided these can be confirmed in a larger series, it would seem clear that a substantial proportion of infants who later develop cerebral palsy are damaged infants from the moment of birth. The observations made in this investigation, as well as those in others, suggest that, in present-day obstetrics, physical trauma at the time of delivery is not a frequent cause of the intrauterine damage these infants evidently sustain. If this be true, there would seem to be only two remaining explanations for intrauterine damage: (1) developmental abnormalities consequent upon unfavorable genetic influences; and (2) pathological alterations of the brain, consequent upon unfavorable intrauterine environment. In regard to developmental abnormalities consequent upon genetic influences, there is little in the literature to support this hypothesis. The neuropathological studies of Courville as well as the experimental observations of Windle indicate that unfavorable intrauterine environment frequently takes the form of hypoxia; and these investigators both believe that fetal hypoxia is a frequent cause of cerebral palsy. Our data on bleeding in pregnancy would be in keeping with this general concept. Certainly, if any obstetrical factor is to be incriminated in the etiology of cerebral palsy, the most likely would seem to be intrauterine hypoxia, consequent upon such factors as sublethal degrees of placental detachment, various anomalies of uterine contractility, and maternal hypotension.

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## ADVANCES IN THE PHYSIOLOGY OF PREGNANCY DURING THE PAST QUARTER CENTURY

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AS THE importance of prenatal care became more widely appreciated in the early decades of this century, many investigators directed their attention toward the adjustments which the maternal organism must make to provide for the sustenance, elimination, protection, and ultimate expulsion of the fetus. Of the pregnancy changes in the mother's physiology, none are more important than those which are related to the blood and circulation for through them are ensured the necessary nourishment of the fetus and the elimination of the waste products of its metabolism. During the past twenty-five years, accordingly, our knowledge of the hemodynamic changes which occur during pregnancy has been greatly enhanced by many contributions concerning the hydremia of gestation and its effect on blood volume and the concentration of the various constituents of the blood.

### Alterations in Blood Volume and Related Changes

Early in this period Dieckmann and Wegner<sup>1</sup> reviewed the previous reports of blood studies made during pregnancy and contributed the findings which they obtained from consecutive observations on the same women in each trimester and during the puerperium. Their Keith-Rountree Congo red determinations<sup>2</sup> indicated that there was a progressive increase in plasma volume which reached its maximum about one month before term when average values were 25 per cent above the levels of the first trimester. In the last month they noted a fall in plasma volume equal to about one-fourth of the total previous gain. This fall continued after delivery until normal values were reached eight weeks post partum. An average increase of 18 per cent in plasma proteins, of 20 per cent in total volume of red cells, and of 15 per cent in the amount of hemoglobin was also observed. Since the increase in each of these constituents of the blood was less than the increase in plasma volume, they noted that a progressive diminution in the concentration of plasma protein, erythrocytes, and hemoglobin accompanied the progressive gain in plasma volume. With the approach of term this trend was reversed and the concentration of all rose as plasma volume declined. These investigators, accordingly, called attention to the fact that red-cell, hematocrit, and hemoglobin determinations, as ordinarily made, are misleading during pregnancy. They also reported a reduction in the electrolyte concentration of the serum. Total base decreased progressively until the last month and at term was 4 to 6 millimolls below normal values. When the total amounts were considered instead of the changes in concentration there was an increase in conductivity and total base of 22.7 per cent and 20.6 per cent, respectively, by the end of gestation. The carbon dioxide of the serum likewise was decreased 4 to 10 per cent by volume below normal values. The acid-base relationship, therefore was one of a compensated alkali or carbon dioxide deficit with the pH of the blood remaining quite unchanged.

While the results of Dieckmann and Wegner's investigations demonstrated trends which have been verified by subsequent workers, some of their values for the various determinations at different periods of gestation were at variance with those obtained by later investigators. Thomson, Hirsheimer, Gibson, and Evans<sup>3</sup> using the Evans Blue modification<sup>4</sup> of the dye method of Keith-Rountree made serial determinations on fourteen pregnant women at six-week intervals from the fifth month to the end of gestation. They also observed plasma volume increases which reached maximum levels in the ninth lunar month but they found the average maximum increase to be 65 per cent higher than the average value in twenty-eight normal nonpregnant women of the same age group. From the hematocrit and plasma-volume values they calculated the average maximum blood and cell volumes to be 45.5 per cent and 16.5 per cent above average non-pregnancy levels. Observations by Roscoe and Donaldson<sup>5</sup> on twenty women in the twelfth, twenty-fourth, and thirty-sixth weeks showed a steady increase in total blood volume which reached an average maximum of about 25 per cent one month before term. In 1948 McLennan and Thouin<sup>6</sup> critically reviewed the work of previous observers and compared the total blood and plasma volumes of twenty women at or near term with determinations made on ten nonpregnant gynecological patients. They found the average increase in plasma and total blood volumes to be 41 per cent and 32 per cent above their control values. This value for plasma volume increase at term was in fairly close agreement with an average gain of 39 per cent at term in twenty-three women which McLennan and Corey<sup>7</sup> reported two years later. Subsequently Caton, Roby, Reid, Caswell, Maletskos, Fluharty, and Gibson<sup>8, 9</sup> and Tysoe, Lowenstein, and Philpott<sup>10, 11</sup> made similar blood and plasma volume determinations on fourteen and ten women, respectively. The first group, using the average thirty-day postpartum value as their nonpregnancy standard, determined the average maximum blood and plasma volume increases to be 45 per cent and 49 per cent of their assumed average nonpregnancy normal blood and plasma volumes. The second group chose the average value obtained at the end of one week post partum as the nonpregnancy basis for calculating the magnitude of the pregnancy increases and reported 34.8 per cent and 44.5 per cent maximum gains in blood and plasma values.

From the foregoing collection of blood and plasma volume studies it is evident that the various investigators who followed Dieckmann and Wegner differed among themselves almost as much as they differed with Dieckmann and Wegner even though all of them followed the original Evans Blue technique or a modification of the same. The Thomson group and the McLennan groups employed the average plasma values of a small number of nonpregnant women as their pregestational standard for the calculation of the percentage increases which occur in pregnancy. Although these standards were almost alike in the three investigations they may have been quite unlike the pregestational values of the women observed during pregnancy, since it is well known that plasma volume varies widely in different individuals. In addition, the Thomson figures represent maximum increases while those of McLennan were obtained at or near term after considerable decline from maximum plasma volume possibly had occurred. The values reported by the Caton group and by Tysoe and his co-workers may be more accurate since in both of these studies average postpartum volumes of the women who were observed during pregnancy were used as their pregestational standards. Had they made their postpartum observations at similar periods in the puerperium, their results probably would have been in closer agreement than were those which they reported. From these excellent and important investigations it is safe to say that plasma and blood volumes increase in pregnancy, that the maximum levels are attained in or near the ninth lunar month, that a significant decline from these maximum levels usually occurs during the last four to eight weeks, and that the maximum increases in blood

and plasma volumes are probably more than 23 per cent and 25 per cent, respectively, and possibly less than 45 per cent and 49 per cent. Until pregestational values, obtained from the same women who are to be the subjects for investigation during pregnancy are used as nonpregnancy standards and a much larger number of consecutive determinations are made on the same women, more definite conclusions cannot be drawn.

The total amount of hemoglobin, as determined by serial estimations on the same women, has been observed to increase during pregnancy to reach an average maximum gain of 12 to 15 per cent at term.<sup>1, 5, 8, 12</sup> Since this increase is much less than the gain in plasma volume, the hemoglobin concentration, as customarily estimated, progressively diminishes and many surveys have shown hemoglobin values of 11 Gm. or less in 50 per cent of the women observed.<sup>12-16</sup>

Numerous studies have revealed the fact that hematocrit and erythrocyte counts decrease progressively as pregnancy advances. Lowest values were reached in the last trimester but a slight rise above minimum levels occurred as term approached.<sup>1, 3, 5, 12, 17, 21</sup> In the third decade of this century these relatively low hemoglobin and red-cell estimations led to the assumption that such findings were evidences of anemia and many references to the so-called "physiological anemia of pregnancy" appeared in the literature of that period.

Total cell volume, when determined indirectly from plasma and hematocrit values, has been shown to increase 16.5 to 20 per cent<sup>1, 3, 5, 6, 10</sup> and the failure of this increase to keep pace with the increase in plasma volume has been suggested as the cause of the low red-cell and hemoglobin values which prevail in pregnancy. On the other hand, the direct method of determining red-cell volume by tagging red cells with radioactive iron has demonstrated that the average maximum increase in red-cell volume is 40 per cent. This value, however, was obtained in the series which showed a 49 per cent average plasma volume increase.<sup>9</sup>

Although a gain of as much as 18 per cent in the total amount of plasma protein has been reported,<sup>1</sup> this gain is considerably less than the increase in plasma volume. As a consequence, a lowering of the concentration of plasma protein has been found to occur commonly in normal pregnancies. The greatest change in this respect takes place early in the last trimester when average values are about 7 per cent below pregestational levels. As term approaches protein concentration gradually increases and normal values are restored by the eighth week post partum. The decrease in the concentration of plasma protein is confined largely to the albumin fraction which falls rather markedly while globulin remains constant or increases slightly and fibrin undergoes a considerable gain which at term may be 20 per cent of the first trimester value.<sup>1, 22-28</sup> Notwithstanding the fact that protein concentration in normal pregnancy is not sufficiently lowered to affect water balance, a slightly inadequate protein intake may augment the deficiency enough to cause considerable edema.<sup>29, 30</sup>

Observations by Feldman and his co-workers<sup>18</sup> on twenty women at monthly intervals revealed an increase in the water content of the blood which reached its highest level about two months before the end of gestation and was accompanied by a progressive decrease in hemoglobin and cell-volume percentage. In the same year Oberst and Plass<sup>31</sup> reported the results of their blood studies in which they found a higher water content of the plasma and lower specific gravity and plasma protein values during the latter part of pregnancy than were observed in the blood of the control women who were not pregnant. These evidences of an increase in the water content of the blood indicate that a definite hydremia is present during pregnancy and that it may be the principal cause of the relatively low plasma protein, red-cell, and hemoglobin concentrations which are observed in most gestations.

Previous concepts concerning pregnancy variations in leukocyte levels have been verified by many observers. All agree that the number of white



cells is normal or moderately elevated prior to the last trimester. In the last trimester a definite increase takes place and average values slightly over 10,000 are observed in the tenth month. A still greater increase occurs immediately before and during labor when it is of sufficient magnitude to render leukocyte counts of little or no value. These alterations in white-cell levels are due to a neutrophilia which is augmented by an increase in lymphocytes near the end of gestation. During labor a lymphopenia accompanies this neutrophilia and alters the differential picture.<sup>21, 22, 32-36</sup>

The suspension stability of the red-blood cells also has been found to be considerably reduced during pregnancy. From rates slightly more rapid than normal in the early months the rapidity of sedimentation may be doubled or trebled by the end of gestation and still further accelerated during the first few days of the puerperium. Because of these changes, a rapid sedimentation rate is of no diagnostic significance prior to, during, and immediately after labor.<sup>18, 37-39</sup>

### The Circulation in Pregnancy

It has been noted by most observers that both the systolic and diastolic blood pressures tend to decrease slightly during the first two trimesters and gradually rise to normal levels at the end of gestation.<sup>40-45</sup> Andros,<sup>46</sup> who was able to compare monthly pregnancy determinations with those obtained from the same women before they became pregnant, noted that the average systolic pressure in three hundred subjects was unchanged until the last month when an increase of only 2.15 mm. occurred. The average diastolic pressure, on the other hand, was 3 mm. below the pregestational level during the first two trimesters and thereafter rose gradually to reach a maximum average increase of 3 mm. above prepregnancy values in the last week. While there was some disagreement as to whether the blood pressure decreases or remains stationary during a normal pregnancy all were in accord concerning the value of a sudden rise in blood pressure in the last half of gestation as an indication of a developing pre-eclampsia. Observations of venous pressure in pregnant women indicate that the pressure in the arm veins remains within normal limits but that the venous pressure in the lower extremities becomes elevated early in the second trimester and rises progressively thereafter as pregnancy advances.<sup>47-49</sup> In a large number of determinations made at term the mean venous pressure of the femoral vein was 24.37 cm. of water. While this pressure is not sufficient to cause the loss of fluid from the blood it may be a factor in the production of edema if some additional alteration in the mechanism of fluid exchange is introduced.

Due largely to the diminution in the concentration of the erythrocytes the viscosity of the blood is decreased. This decrease has been found to be a progressive one up to one month before term when the lowest viscosity values average 12 per cent below normal.<sup>44-50</sup> Even though the viscosity of the blood is diminished the work of the heart is increased. A number of investigators<sup>50-55</sup> have reported accelerations of from 25 to 50 per cent in the cardiac output. Hamilton, by means of catheterization of the right side of the heart, found that the minute output rose rather rapidly late in the first trimester and continued to rise at a more gradual rate thereafter until the ninth month at which time average cardiac output was 27 per cent above the nonpregnancy level. It then declined to levels slightly above normal at term. In many of the subjects investigated during the last trimester rhythmic fluctuations in the venous filling pressure were observed. These coincided with the contractions of the uterus. The pressure rose 4 to 10 cm. of saline as the uterus contracted and fell as it relaxed.

Because a number of the circulatory changes which occur during pregnancy are similar to those which are caused by a large arteriovenous fistula, it has been suggested that they too are due to a modified arteriovenous shunt at the placental site.<sup>48, 50, 56</sup> Anatomical support for this hypothesis is furnished by the fact that blood from the spiral arteries passes through the intervillous space to the marginal sinus and thence into the uterine veins without the intervention of a capillary system.<sup>57, 58</sup> It is also favored by the observation that blood taken from the uterine veins of animals has more oxygen than the blood from the right ventricle.<sup>59, 60</sup> If this is the true cause of the pregnancy alterations in the circulation prior to the ninth month, however, some additional explanation must be found for the reduction in blood volume and cardiac output which takes place toward the end of gestation.

From the foregoing synopses of the contributions which dealt with the pregnancy changes in the blood and circulation, it may be concluded that the greatly expanded vascular system of the gravid uterus takes up a progressively increasing proportion of the blood in the general circulation. To supply this extra requirement adequately the volume of circulating blood is augmented by a considerable increase in its water content and an increase in varying lesser degrees in the total amount of hemoglobin, red cells, plasma protein, and other components of the blood. The resulting diminutions in the erythrocyte, hemoglobin, and protein concentrations are not sufficient to affect the well-being of the mother or her unborn child but are capable of favoring the development of anemia and water retention whenever the intake of some of the essential nutrients is deficient. Despite the fact that the disproportionate increase in water content diminishes the viscosity of the blood, the augmented blood volume places an added burden upon the heart. Ordinarily the normal pregnant woman's cardiac reserve is ample to enable her heart to handle this added burden with a commensurate increase in cardiac output. In cardiac patients, on the other hand, the extra load may cause a break in compensation. In such individuals the danger of congestive failure during pregnancy rises and falls to a considerable extent with the rise and fall in blood volume.<sup>61</sup>

### Physiology of the Gravid Uterus

Important contributions concerning the anatomy and physiology of the gravid uterus have thrown light upon the architecture of the uterine musculature, the behavior of the isthmus during pregnancy, the circulation at the placental site, and the influence of uterine growth, enlargement, and shape on the blood supply to the placenta. By means of a special method of preparation and the use of an oblique lighting arrangement Goerttler<sup>62</sup> observed that the myometrium is composed mostly of muscle fasciculi which cross at angles that vary at different levels. In the fundus they interlace at right angles. As the distance from the tubal junctions increases the angles of intersection become wider and wider and are almost 180 degrees at the isthmus where the fasciculi are more nearly parallel and much less interwoven than in the region of the fundus. These observations led him to suggest that the greater part of the myometrium develops from the circular layer of the Müllerian ducts and that the particular angles of intersection of the muscle fasciculi at the various levels are due to the different degrees of obliquity of the converging ducts at those levels when fusion occurred. He assumed that the intricate network of the greater part of the myometrium is made up of two interlacing spiral systems of muscle fasciculi, the arrangement of each spiral system being that which is observed when the upper part of a spiral spring is elevated while the lower part remains stationary or fixed. With such an arrangement of the thick middle layer of the uterine musculature, a contraction wave starting near the

attachment of the tubes should shorten the transverse, anteroposterior, and longitudinal diameters just as the contraction of a circular and a longitudinal system of muscles would shorten all of these diameters if the circular and longitudinal muscles contracted simultaneously. Since this is the well-known effect of a uterine contraction and since all who have attempted the dissection of a full-term uterus must know that whatever longitudinal muscle is demonstrable is too meager to shorten the longitudinal diameter of the uterus, Goerttler's suggestion deserves serious consideration. His work should encourage other investigators to attempt its corroboration or find a suitable substitute for the faulty concept of this aspect of uterine physiology which has been accepted too long by most obstetricians.

Reynolds,<sup>63, 64</sup> in his investigation of the effect of distention on the growth of uterine tissue in the rabbit, observed that maximum growth was attained when the conceptus was spheroidal in form and the resistance of the uterus to enlargement by the conceptus was thus equal in all directions. On the other hand, when the conceptus became elongated and assumed a more cylindrical shape, resistance to longitudinal enlargement was diminished and the rate of growth of the uterine tissue decreased with the result that further enlargement of the uterus was accomplished principally by stretching rather than growth of its wall. It was noted that the transition from the spheroidal to the cylindrical form took place about the twenty-second day, i.e., about the beginning of the third trimester. The effect of the change in shape on the flow of maternal blood in the uterus was also studied. As the uterus grew under the stimulus of distention by a spheroidal conceptus, the rate of flow gradually decreased to 68 per cent of the pregestational rate on the twentieth day. Just before the transition from the spheroidal to the cylindrical form, two days later, a further and profound drop in the circulation rate occurred. Following conversion from spheroid to cylinder the rate rapidly recovered to 75 per cent of its early pregnancy level.<sup>65, 66</sup> This finding led Reynolds<sup>67</sup> to suggest that the ischemia which is present at the time of conversion may have a deleterious effect on the mother or fetus or both.

Roentgen observations on the changes in the shape of the uterus in the monkey indicate that a similar conversion from a spheroidal to a cylindrical form takes place around the hundredth day of gestation which in the monkey is very near the end of the second trimester. It likewise was found that the curve of uterine growth flattens out and the curve of fetal weight rises sharply after that time.<sup>68</sup> From serial soft-tissue x-ray studies of fifteen pregnant women, Gillespie<sup>69</sup> concluded that a somewhat similar change in the shape of the human uterus occurs soon after the twentieth week, following which uterine growth decreases and fetal weight rapidly increases. He, accordingly, called attention to the possibility that a diminished vascularization of the myometrium during the growth period might lead to an inadequate blood supply to the placenta in the last half of pregnancy when the enlargement of the uterus is accompanied by a progressive stretching of its wall. This, no doubt, is an important implication for those who regard uterine ischemia as a factor in the etiology of eclampsia and premature delivery.

Roentgen studies by Beker<sup>70</sup> of specimens injected with radiopaque material and corrosion preparations of Kearns<sup>71</sup> have shown that the uterine and ovarian arteries are increased in diameter, length, and tortuosity. Early in pregnancy the branches of the main trunks are increased in number and in size. They spread out radially over each side of the uterus and extend like a canopy over the fundus but do not cross the midline. Later the circulation at the placental site continues to expand while that of the remainder of the uterus is relatively diminished. The greatly enlarged anastomosing veins



which receive blood from the placenta and uterus have an aggregate diameter much larger than the veins into which they empty. They thus serve as safety devices which allow the blood forced from the placental site to collect in their expanded channels before emptying into the narrower iliac veins.<sup>59, 72</sup> In 1935 Spanner<sup>73</sup> revolutionized our thinking concerning the circulation at the placental site. He stated that the distal portions of the spiral arteries become dilated and terminate in funnel-shaped openings in the floor of the intervillous space, that only the trunks of major villi traverse that portion of the intervillous space which is beneath the chorionic plate while the terminal villi are massed at the opposite pole of the placenta, that the intercotyledonary septa end a considerable distance below the chorionic plate, and that drainage from the intervillous space is solely through the marginal sinus which connects with the network of veins beneath the placenta. According to his view, maternal blood from the openings of the spiral arteries in the floor of the intervillous space, after bathing the dense mass of villi adjacent to the decidua, flows toward the chorionic plate. From there it is deflected laterally to drain into the marginal sinus and thence into the maternal veins. Since the flow of blood from the spiral arteries through the intervillous space and back into the veins of the mother takes place without the intervention of a system of capillaries, the circulation of blood at the placental site is thought to be analogous to that which occurs at the site of a large arteriovenous fistula but modified by the resistance of the mass of villi adjacent to the floor of the intervillous space. While other observers have corroborated most of Spanner's findings, not all of them<sup>73-76</sup> agree that drainage from the intervillous space is limited entirely to that which takes place through the marginal sinus. The circulation at different stages in gestation in the monkey has been carefully investigated by Ramsey.<sup>74</sup> She observed marked elongation of the spiral arteries with extensive coiling and back-and-forth looping up to the end of the first trimester. Toward the end of the second trimester, when the spheroidal conceptus takes on a more cylindrical form, the coils pay out and disappear. As the uterine wall becomes increasingly stretched the arteries become more and more compressed and as a consequence appear as rather broad and flattened ribbonlike structures during the last half of the third trimester.

### The Cervix in Pregnancy

From his study of a number of pregnant and nonpregnant uteri Danforth<sup>77</sup> has added to our knowledge of the behavior of the cervix and isthmus during pregnancy. According to his observations the wall of the cervix is made up almost entirely of connective tissue. Not more than 15 per cent is muscle and nothing suggestive of a muscular sphincter is demonstrable. During early pregnancy the length of the cervix is not significantly altered. On the other hand, the isthmus is made up mostly of muscular elements which undergo hyperplasia and hypertrophy like the remainder of the myometrium. It becomes elongated to three times its former length in the third month. Thereafter, as the products of conception grow and require more space the isthmic musculature unfolds and the isthmus becomes incorporated into the general body cavity.

In 1927 Stieve<sup>78</sup> reported the results of his extensive investigations and described the progressive changes which he observed in the blood vessels and mucosa of the cervix. He showed that the blood vessels, which in the non-pregnant cervix were small and relatively sparse, became more numerous and greatly enlarged. The increase in vascularity was so marked in some women that the cervix at term was almost cavernous. This vascular engorgement was regarded as an aid in keeping the cervix closed throughout pregnancy and



its disappearance during labor was thought to facilitate dilatation. The mucosa was observed to grow in thickness until it made up almost half of the cervix at the end of gestation and the number, size, and activity of the glands were markedly increased. Recent interest in intraepithelial carcinoma has encouraged many<sup>79-86</sup> to restudy the pregnancy changes in the cervical epithelium. While the epithelium of the nonpregnant cervix is not sufficiently responsive to hormone stimulation to show cyclic changes comparable to those which occur in the endometrium during the menstrual cycle, the effect of the great hormone increase in pregnancy on the cervical epithelium in many cases is pronounced. As a result, transformation of the surface columnar into transitional or stratified columnar epithelium and piling up of the intra-glandular epithelium is much more frequently observed in the pregnant than in the nonpregnant cervix. Likewise, thickening of the stratified squamous epithelium of the portio vaginalis is more widespread and in not a few instances there is a hyperactivity of the basal cells of varying degrees. This may consist of only a slight increase in the number of cells with the formation of a layer several cells thick and no other change. In rare instances the increase may be sufficiently marked to make up half or more of the epithelium with hyperchromatosis of the nuclei and many mitotic figures. It may then be difficult to differentiate between this hormone-stimulated hyperactivity which retrogresses after delivery and a true intraepithelial carcinoma which ultimately may become invasive.

### Metabolism in Pregnancy

In their effort to show the presence or absence of a relationship between weight gain and certain complications of pregnancy and labor, a number of writers<sup>87-94</sup> have reported their observations concerning the weight changes in both normal and abnormal pregnancies. An excellent analysis of these and older reports by Chesley<sup>93</sup> appeared in 1944 and made easily available a wealth of data on the subject. According to these data the weight remains stationary or falls off slightly in the early weeks. Thereafter, it increases until shortly before the end of gestation when a loss of 1 to 2.5 pounds not infrequently occurs. During the last trimester the rate of gain was 0.86 pounds per week in 13,500 cases and the average total gain was 24 pounds in 11,900 pregnancies. For their standard of normality in a meticulous investigation of the subject, Tompkins and Wiehl<sup>95</sup> plotted a curve which represented the average weekly cumulative gain in sixty women who were specially selected from a group of six hundred because their prepregnancy weights were within 10 per cent of the standard weight for their heights and because their pregnancies were totally uncomplicated and resulted in the birth of living full-term infants. The gain in the first, second, and third trimesters averaged 3, 10.8, and 10.2 pounds, respectively. The average total gain was 24 pounds and the average weekly increment was 0.86 pounds per week. The gain in women who were underweight before they became pregnant was more than normal and less than normal in those who were overweight.

The effect of thyroid disorders on pregnancy led to a renewed interest in the establishment of standard values for the basal metabolic rate at different periods of gestation.<sup>96-102</sup> Although marked variations have been noted, systematic determinations made on the same patients at regular intervals throughout pregnancy have shown that the rate rises as pregnancy advances. From average values around minus 5 in the first trimester it increases to around plus 10 at term. This increase of approximately 15 per cent corresponds to the average gain in weight during pregnancy. The greatest gains in metabolic rate have been observed in those women whose rates were low prior to the onset of gestation.<sup>101</sup>

Hunscher and her associates<sup>103</sup> in 1933 compiled the results of 945 nitrogen balances obtained from the third to the tenth months of pregnancy. These showed a slightly negative balance in the fourth month and a gradually increasing retention thereafter, with an average total nitrogen storage of 514.9 Gm. for the last eight months of gestation. The daily increment rose from 1.99 Gm. in the fifth month to 3.46 Gm. in the tenth and averaged 2.28 Gm. Similar retentions have been subsequently observed by other investigators.<sup>104-108</sup> These balance studies indicate that at least 15 Gm. of protein of high biological value must be added to the diet of the average woman when she becomes pregnant to provide a daily nitrogen increment of 2.28 Gm. They also show that the mother retains approximately 375 Gm. more than are required to provide for the needs of the fetus, the placenta, and the growth of the uterus and breasts.

Balance studies have also shown that a daily intake of 1 Gm. of calcium in the first trimester and  $1\frac{1}{2}$  Gm. thereafter is sufficient to maintain a positive balance throughout pregnancy.<sup>104-108</sup> During the last three months, when the fetus takes up almost five-sixths of its calcium and the mother's retention is greatest, the average daily increment is 0.222 Gm. While the total amount retained, approximately 30 Gm., is more than enough to supply the  $22\frac{1}{2}$  Gm. which the fetus requires, it is quite inadequate to satisfy the added requirements of lactation. Many observers have noted that exposure to sunshine and the addition of vitamin D to the diet increase the calcium content of the fetus.<sup>109, 110</sup>

According to observations made with radioactive iron, a pregnant woman absorbs two to ten times the amount of iron usually taken up by the non-pregnant woman<sup>114</sup> and balance studies have shown that more of it is retained than is excreted. The greatest retention is in the second trimester when the fetal needs are minimal but the number of maternal red cells is progressively increasing. During the last two months, the period in which the fetus takes up 67 per cent of its iron, the mother's daily increment is insufficient to supply the fetal needs and she must draw upon her previously stored iron.<sup>105, 108, 110</sup>

### The Placental Hormones

The demonstration of an estrogenic hormone in the ovarian follicle by Allen and Doisy<sup>163</sup> in 1922 stimulated a vast amount of productive research concerning the relationship of the endocrines to pregnancy. In 1925 Frank and his associates<sup>115</sup> discovered the stimulating effect of estrogen on the myometrium in an experiment in which they administered follicular fluid to castrated rats and noted that the subsequently excised uteri contracted in a manner similar to that which occurs in uteri removed from rats in estrus. Two years later Aschheim and Zondek<sup>116</sup> found estrogenic and gonadotrophic substances in the urine of pregnant women and in the following year reported<sup>117</sup> the results of their urinary estrogen assays in the different periods of gestation. About the same time Weichert<sup>118</sup> artificially produced deciduomas in oophorectomized animals by inducing estrus with estrogen and administering corpus luteum extract after he had traumatized the uterus. Soon thereafter Corner<sup>119</sup> demonstrated the presence in the corpus luteum of a hormone which was capable of causing progestational changes in the endometrium and he gave it the name progestin. Subsequently Allen and Corner<sup>120</sup> proved that progesterone was necessary for the maintenance of pregnancy when, by the administration of their corpus luteum extract, they prevented the interruption of pregnancy after oophorectomy in the rabbit, an animal in which oophorectomy during pregnancy is always followed by resorption or abortion of the conceptus. In the same year Doisey and his co-workers<sup>121</sup> reported the successful preparation of crystalline estrogen from the urine of pregnant

women and by 1932 Allen<sup>122</sup> was able to produce progesterone in crystalline form. In the meantime Knaus<sup>123</sup> and Reynolds<sup>124</sup> published the results of their studies concerning the effect of the corpus luteum on uterine motility in which they observed that corpus luteum extract inhibited uterine contractions in the rabbit. This effect of progesterone was disputed by Schultze<sup>125</sup> and thus was precipitated a controversy which has persisted to the present time. A number of workers<sup>126-131</sup> using the same and different animals have agreed with Knaus and Reynolds while others<sup>132-137</sup> have made contradictory observations. From the foregoing brief and incomplete references to some of the important contributions to our knowledge of the endocrines in pregnancy it is evident that the decade from 1925 to 1935 was extraordinarily productive in this respect. During this brief span it was established that estrogen and gonadotrophin were present in the urine,<sup>116</sup> blood,<sup>138</sup> and placenta,<sup>139-142</sup> and that the placenta was the chief source of these hormones and progesterone.<sup>143-145</sup> It was also found that removal of the ovaries after the first trimester did not lessen the excretion of estrogen in the urine<sup>146-148</sup> and did not eliminate the progesterone influence with regard to the maintenance of pregnancy.<sup>149-151</sup>

In 1937 Browne and Venning<sup>152</sup> published their method of estimating progesterone excretion by means of pregnanediol determinations and noted that the excretion of pregnanediol increases from 5 to 10 mg. in early pregnancy to 105 mg. by the eighth month. Their assays of estrogen in the urine,<sup>155</sup> as well as the urine<sup>117, 154, 155</sup> and blood<sup>155-157</sup> assays of other investigators indicated that the production of estrogen followed a similar course and reached maximum levels at term. On the other hand, urine<sup>155, 158, 159</sup> and blood<sup>155, 156-162</sup> assays of gonadotrophin showed that the production of this chorionic hormone increases very rapidly near the end of the second month and reaches its highest level within a short time. Thereafter it drops rather sharply to its former relatively low level at which it remains throughout the last two trimesters.

Although these remarkable endocrine studies have contributed much to our knowledge of the physiology of reproduction, they not only have failed to solve some of the problems which the practical obstetrician had hoped they might solve but the conflicting results of their application to these problems has led to much confusion. Estrogen as a hoped-for myometrial stimulant has failed to be of value in the induction of labor and in the treatment of uterine inertia and more and more obstetricians have come to question the value of progesterone as a preventative of abortion and premature labor. On the other hand, the discovery of chorionic gonadotrophin in the blood and urine of pregnant women has been of great practical significance in that it has led to the development of a number of valuable pregnancy tests. Perhaps, when more work in this connection is done, our general disappointment with respect to the usefulness of our present knowledge of the endocrines in pregnancy will give way to an approbation similar to that which arose when the Ascheim-Zondek test for pregnancy was first introduced.

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## THE CAUSES OF HISTIDINURIA IN NORMAL PREGNANCY\*

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**D**URING normal pregnancy, there is an increased excretion of almost all of the essential amino acids.<sup>1</sup> Of these, histidine has attracted more attention than any other, perhaps more than it deserves, chiefly because in 1908 Knoop<sup>2</sup> discovered a reaction between bromine and histidine which formed the basis for a simple colorimetric determination. Increased quantities of histidine were found in pregnancy urine by Honda<sup>3</sup> in 1923, and the occurrence of increased histidinuria was proposed as a chemical test for pregnancy by Voge<sup>4</sup> in 1929. There was little interest in the subject, however, until Kapeller-Adler<sup>5</sup> improved the bromination method in 1933 and again urged its use for the diagnosis of pregnancy. Since then, scores of articles have appeared in the European and American literature either denying or reaffirming the diagnostic value of the test. Although histidine appears to some degree in all urine specimens, the colorimetric procedure gives negative results in 88 per cent of nonpregnant women and 86 per cent positive results in pregnant women, based on a survey of the literature as previously reported.<sup>6</sup> In the meantime, improvements in the rapid and more accurate diagnosis of pregnancy through biologic tests for chorionic gonadotrophin have overshadowed the various chemical tests, and the emphasis has shifted more to a search for the cause—or causes—of histidinuria in normal pregnancy and the reasons for its disappearance in pre-eclampsia.

The first serious hypothesis as to the cause of pregnancy histidinuria was that of Kapeller-Adler<sup>7</sup> who, in 1935, proposed that liver histidase was inhibited by chorionic gonadotrophin. This was based on the finding of reduced histidase activity of liver tissues obtained at autopsies on pregnant women (an observation which could not be confirmed by Edlbacher and Heitz<sup>8</sup>), and an in vitro inhibition of liver cells (but not purified histidase) by chorionic gonadotrophin.<sup>9</sup> In 1943, we<sup>6</sup> objected to this hypothesis, partly on the grounds that the curve of increased histidine excretion followed the curve of increased steroidal hormones rather than that of chorionic hormone; that is, the histidinuria reached a peak during the seventh and eighth months of pregnancy, rather than during the first trimester, and declined during the two or three weeks prior to labor.

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In 1946, we<sup>10</sup> proposed an alternate hypothesis, namely, that the histidinuria of normal pregnancy was due to an increased renal clearance of histidine, secondary to a diminished rate of renal tubular reabsorption. This was based on observations following the single intravenous administration of L-histidine, which resulted in high urinary excretion rates at relatively low plasma levels. We also concluded that the injected histidine disappeared from the blood stream with the same rapidity in pregnant as in nonpregnant women. Diazotized p-chloroaniline was employed for the colorimetric determination of the plasma histidine. These findings were subsequently disputed by Kapeller-Adler,<sup>11</sup> who, using sulfanilic acid and sodium nitrite for determining plasma histidine, described considerable delays in the rate of disappearance of injected histidine during normal pregnancy. Whether this might be due to the difference in reagents used is problematical, since neither one is specific for L-histidine. Accepting her data relative to the blood curves (for they are based on a larger number of cases), we agree that there must be a reduced "metabolism" of histidine in pregnancy. On the other hand, an application of the conventional  $\frac{UV}{P}$  formula to those same data reveals the fact that one hour after injection the kidneys of her nonpregnant subjects were clearing only 2.2 to 4.4 ml. plasma of histidine per minute while the normal pregnant subjects were clearing from

#### HISTIDINE

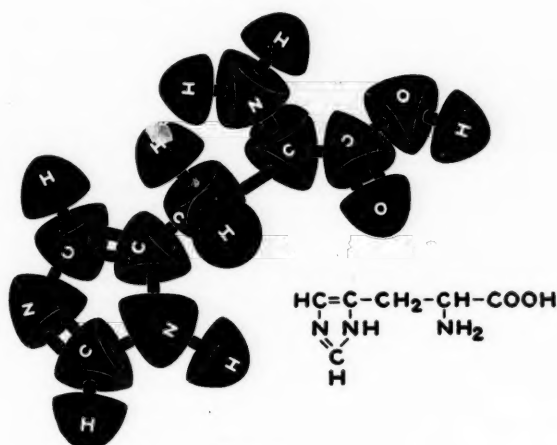


Fig. 1.

18 to 24.7 ml. plasma of histidine per minute. This supports our previous finding, but leads to the conclusion that there must be multiple causes for the histidinuria of pregnancy. The present study was designed to evaluate quantitatively each of the possible mechanisms.

#### Metabolism of L-Histidine

The naturally occurring L-histidine (Fig. 1) is an amino acid essential for normal growth and development. Although it is an important constituent of proteins, it is of interest to note in passing that the human placenta has a lower



proportion of histidine in its proteins than any other tissue studied. Recent investigations indicate that the primary catabolic pathway of metabolism involves first a removal of the  $\alpha$ -amino group by histidase to form urocanic acid, which is then broken down by urocanase to form one molecule each of L-glutamic acid, formic acid, and ammonia.<sup>12, 13</sup> There are two alternate pathways of metabolism which are possible: an oxidation by L-amino acid oxidase to form imidazole-pyruvic acid, or a decarboxylation by histidine decarboxylase to form histamine. The extent to which these two possible catabolic pathways occur in the body is not known. A major portion of available histidine, of course, goes into protein synthesis, and a relatively large portion is excreted unchanged into the urine.

*What Are the Possible Immediate Causes of Increased Histidinuria?*

The following list would appear to exhaust all of the possible mechanisms which might account for an increased excretion of any amino acid:

1. An increased rate of glomerular filtration.
2. A decreased rate of renal tubular reabsorption.
3. An increased rate of gastrointestinal absorption.
4. A decreased rate of metabolism because of: (a) diminished utilization, or (b) slower destruction, or both.

The following studies will show that the first, second, and fourth factors are all operative in causing the histidinuria of normal pregnancy. Data on subjects with pre-eclampsia will be presented elsewhere.<sup>14</sup>

### Methods

Ten healthy, volunteer subjects were studied during periods of pregnancy ranging from 2 to 10 weeks before delivery, and the same subjects were restudied 4 to 7 weeks after delivery. Each patient, therefore, served as her own control, and inasmuch as the methods employed were identical in all instances, the only major variable was the presence or absence of pregnancy. Each subject was admitted to the ward in a fasting state, with water ad libitum, and an indwelling catheter was placed. An intravenous infusion of 5 per cent dextrose in water was adjusted to a constant rate of 4 ml. per minute by the use of a microregulator. A priming dose of 3 Gm. of inulin was given followed by a maintenance dose of 56 mg. per minute. The priming dose of L-histidine hydrochloride (expressed as histidine base) was 500 mg. (3.2 millimols) and the maintenance dose was 12.2 mg. (0.08 millimol) per minute. After the lapse of 20 minutes for equilibration, blood and urine samples were collected for three consecutive periods of 20 minutes, following the methods described by Goldring and Chasis.<sup>15</sup> Inulin was determined by the method of Roe, Epstein, and Goldstein,<sup>16</sup> and the plasma and urinary levels of histidine were determined microbiologically, using the organism *Leuconostoc mesenteroides*. The average of the three clearance periods was corrected to 1.73 sq. M. of body surface using the actual body weight on the day of the test. (There are physiologically sound reasons for using only the nonpregnant weight for the same individual, but this would exaggerate the differences found, and, being unconventional, might be objected to by some investigators.)

### Results

#### *Is There an Increased Rate of Glomerular Filtration?*

Considerable increases in the glomerular filtration rates for inulin (and therefore for water and amino acids) were found during normal pregnancy, as shown in Fig 2. These increases were noted in all 10 subjects, an event which should not occur by chance more often than once in 1,024 samplings of the population from a purely directional standpoint alone and without regard to the magnitude of the change. Since this finding is at variance with many of the data reported prior to 1950, and inasmuch as the observation has physiologic implications of far greater importance than its application to the clearance of histidine, some explanation is in order. Our data on glomerular filtration rates are in agreement with the recent studies of Bucht<sup>17</sup> and of Bonsnes,<sup>18</sup> which are compared with this study in Table I. These two workers have also found that the renal blood flows (measured by para-aminohippurate clearances) increase in proportion to the glomerular filtration rates, thus maintaining a constant filtration fraction. Both values, however, return almost to the nonpregnant levels during the last lunar month of pregnancy, which is the time in pregnancy when most previous studies were conducted. This is probably the most important factor accounting for the discrepancy.

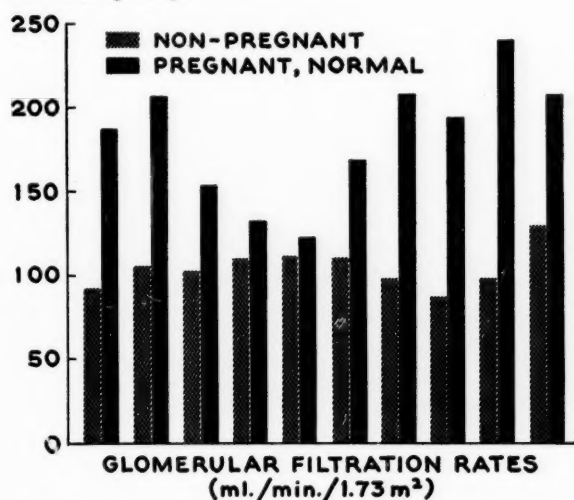


Fig. 2.—Each pair of bars represents one individual. In all bar graphs the 10 individuals are arranged in the same order.

The kidneys of women at the seventh or eighth month of pregnancy thus filter about 250 to 300 L. of water and solutes each day instead of the nonpregnant amount of 150 to 175 L. daily. In the case of freely soluble, small molecular solutes, it may be assumed that the concentration of histidine in the glomerular filtrate is the same as its concentration in the plasma. The absolute clearance of histidine is dependent upon the proportion of the amount filtered which is reabsorbed by the renal tubules. The histidine clearance values for the same ten individuals are shown in Fig. 3, and are markedly greater during pregnancy than after delivery in all ten individuals.

TABLE I. INULIN CLEARANCES IN NORMAL PREGNANCY

	BUCHT <sup>17</sup>			BONSNES <sup>18</sup>			THIS STUDY		
	NO.	MEAN	S.D.	NO.	MEAN	S.D.	NO.	MEAN	S.D.
Nonpregnant	23	122	±24	8	119	±4	10*	104	±12
Pregnant 12 to 35 weeks	23	169	±27	13	183	±20	10*	171	±39
Pregnant 36 to 41 weeks	9	157	±28	12	129	±43	-	-	-

\*These represent the same 10 individuals. Values are expressed in milliliters per minute per 1.73 sq. M. plus or minus one standard deviation.

### *Is There a Diminished Percentage of Histidine Reabsorbed by the Renal Tubules?*

By comparing Figs. 2 and 3, it can be seen that the clearance of histidine is relatively greater than the glomerular filtration rate. Dividing the first by the second, and multiplying by 100, gives the percentage of filtered histidine which escapes renal tubular reabsorption. These values are shown in Fig. 4.

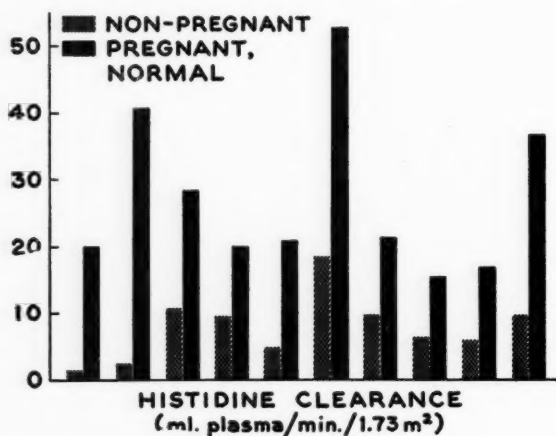


Fig. 3.

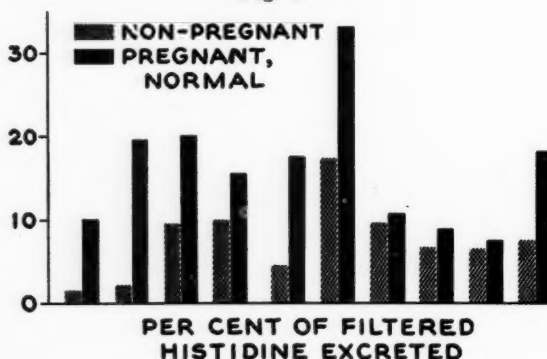


Fig. 4.

Although the differences are small in some cases, the direction of change is the same in each—again an event which could hardly occur by chance. If, during normal pregnancy, the renal tubules continued to reabsorb the same percentage of histidine delivered to them, each pair of bars would be exactly the same height.

The diminished tubular reabsorption might theoretically be due to the increased load, that is, an approach toward a theoretical  $T_m$  or maximal reabsorptive capacity for histidine. This seems highly unlikely in view of the fact that Pitts<sup>19</sup> was unable to demonstrate a  $T_m$  for histidine in the dog at any technically feasible plasma level. It appears, therefore, that there is an inhibition of the renal tubular reabsorptive mechanism for histidine in normal pregnancy, and that this is an important factor in accounting for the increased quantities of histidine excreted.

*Is There an Increased Rate of Gastrointestinal Absorption?*

This question, not pertinent to the present study because the gastrointestinal tract was by-passed, might be raised in connection with the endogenous histidinuria of pregnancy. It may be answered clearly in the negative as the result of our<sup>10</sup> previous finding that following the ingestion of 3 Gm. of histidine, the plasma level rises more rapidly (and to a higher level) in the nonpregnant woman.

*Is There a Decreased Rate of Metabolism for Histidine in Normal Pregnancy?*

In using the word metabolism, we refer to the sum of anabolic and catabolic processes, for we have no way of distinguishing between the two. In 8 of our 10 subjects, we observed that the plasma levels of histidine during pregnancy were higher during the period of constant infusion than they were after delivery. The plasma inulin levels, on the other hand, were always significantly lower. The latter could be anticipated, of course, because the distribution volume is larger during pregnancy and the rate of excretion is higher. The same two factors operate in the case of an amino acid; so the finding of elevated histidine levels is certainly an indication of a reduced rate of metabolism.

In order to learn the magnitude of this change, the following formulas were derived:

$$(1) P_H = \frac{H - 0.06 (UV)_H - M}{D} \text{ in which } P_H \text{ represents the plasma level}$$

of histidine maintained during the infusion; H is the total quantity of histidine delivered intravenously, expressed in grams per hour; the expression  $0.06 (UV)_H$  is the quantity of histidine excreted in grams per hour; the symbol M is the sum of metabolic processes; and D is the volume of distribution for inulin (not for histidine).

$$(2) P_I = \frac{I - 0.06 (UV)_I}{D} \text{ is the same equation in which the same symbols}$$

are used for inulin. (The M is omitted since there is no metabolism of inulin.)

The value for D was not determined and therefore represents an unknown dilution factor. Dividing the first by the second equation permits one to cancel D, resulting in the following equation:

$$(3) \frac{P_H}{P_I} = \frac{H - 0.06 (UV)_H - M}{I - 0.06 (UV)_I} \text{ in which all values are known except M.}$$



The absolute value of  $M$  is literally that quantity of histidine each hour which enters the space in the body not occupied at that moment by inulin. Inulin is known to remain in the extracellular compartment of the body; so we may redefine  $M$  as *that quantity of histidine which enters the intracellular compartment of the body each hour during the infusion*. What happens to the amino acid after it enters the cell is, of course, not elucidated by this analysis.

The values for  $M_n$  (nonpregnant status) and  $M_p$  (pregnant status) are given in Table II.

The difference between the means is statistically significant. Although there is no precedent (that we are aware of) for calculating the rate of metabolism for any amino acid in a human subject, we believe that this analysis establishes the fact that the rate of utilization and/or destruction of histidine is reduced during normal pregnancy.

TABLE II. RATES OF METABOLISM FOR HISTIDINE IN THE NONPREGNANT AND PREGNANT STATES

PATIENT	$M_n$ (GM./HR.)	$M_p$ (GM./HR.)	PERCENTAGE CHANGE
1	0.99	1.04	+5
2	1.00	0.73	-27
3	1.03	0.67	-35
4	1.04	0.73	-30
5	0.99	0.92	-7
6	0.94	0.96	+2
7	1.06	0.54	-49
8	1.01	0.84	-17
9	1.09	0.86	-21
10	1.00	0.81	-19
Mean	1.015	0.81	-20
S.D.	$\pm 0.04$	$\pm 0.15$	$\pm 16.1$

### Comment

The ultimate means by which normal pregnancy effects an increased glomerular filtration, a diminished tubular reabsorption, and a reduced rate of metabolism for histidine are not known. It would be reasonable to suggest, however, that all three changes are brought about by the influence of steroid hormones. Stephens and associates,<sup>20</sup> for example, reported striking increases in the histidine excretion of patients being treated with ACTH and cortisone. It has also been observed<sup>21</sup> that the same hormones cause an elevation in the glomerular filtration rate and renal blood flow of normal man. We are currently investigating the effects of adrenal cortical steroids on the filtration, reabsorption, and metabolism of histidine in an attempt to learn if the effect of normal pregnancy upon these factors can be reasonably well reproduced in nongravid subjects by hormonal therapy.

The absolute values for the rates of glomerular filtration, tubular reabsorption, and metabolism do not indicate the relative importance of each in causing the increased histidinuria of pregnancy. This can be estimated by a series of calculations in which two of the three factors are kept constant (at the nongravid rate) and the third altered to the rate observed during pregnancy. In this manner, it was found that all three factors are quantitatively significant,

but that the relative magnitude varies considerably from one individual to the next. When one realizes the large number of events capable of altering the glomerular filtration rates from hour to hour in the same person, it is reasonable to assume that the relative importance of the etiological factors causing histidinuria varies from day to day in the same individual.

By utilizing averages, it appears that the increased rate of glomerular filtration accounts for about half of the excess histidine excreted, while the tubular and metabolic factors each account for about one-fourth of the amount.

Whether the decreased rate of metabolism reflects an inhibition of histidine breakdown or not is unknown. There is no valid reason for assuming that there is an inhibition of liver histidase in pregnancy, because the observed effect might just as well be due to a decrease in the rate at which histidine is incorporated into newly formed peptides and proteins.

### Summary

Renal clearance studies were conducted on 10 normal pregnant women who were receiving intravenous infusions of inulin and L-histidine at a constant rate. The plasma and urinary levels of the amino acid were determined microbiologically. Identical studies were repeated on the same individuals four to seven weeks after delivery.

All subjects had increased histidinuria while pregnant, with marked increases in histidine clearance. Three factors were found to account for this:

1. The rate of glomerular filtration was increased in all 10 subjects from a nonpregnant mean of 104 to a pregnancy mean of 171 ml. per minute per 1.73 sq. M. of body surface. This change accounted for about half of the excess histidine excreted.

2. The percentage of the filtered histidine which was reabsorbed by the renal tubules was decreased during pregnancy in every subject, accounting for about one-fourth of the excess histidine excreted.

3. The rate at which the injected histidine entered the intracellular compartment of the body was decreased by pregnancy from a mean of  $1.015 \pm .04$  to a mean of  $0.81 \pm 0.15$  Gm. per hour. This reduction, statistically significant, causes an elevation of the plasma histidine level sufficient to account for the remainder of the excess histidine excreted. It is not known whether the altered metabolism is due to a decrease in the rate of histidine breakdown, or in the rate of histidine utilization, or both.

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## ALTERATIONS OF POTASSIUM METABOLISM IN PREGNANCY

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IT IS now apparent that deviations in both the concentration and distribution of potassium in the body fluids may affect the health of the individual and under extreme circumstances may result in death.<sup>1-4</sup> The consequences of either depletion or excessive accumulation of potassium have been observed in a variety of medical and surgical situations.<sup>5-8</sup> Alterations in potassium metabolism have been encountered in pregnancy as well. It is the object of this report to direct attention to the potential dangers of hypokalemia or hyperkalemia as encountered in the obstetrical patient. It is not intended to imply that potassium imbalance is a consistent complication of these several obstetrical conditions. In the cases presented, however, the most urgent clinical problem was directly related to deviations in the cellular and extracellular content of potassium.

Because of the positive sodium balance in normal pregnancy, hypokalemia might be more easily produced under conditions of poor potassium intake and prolonged vomiting. Furthermore, the alkalosis that may be produced by vomiting in itself may aggravate continued urinary losses of potassium. Severe states of potassium depletion in pregnancy, while unusual, are frequent enough to be a source of real concern to those who must diagnose and treat disorders of fluid and electrolyte balance in pregnant women. By contrast, where kidney function is acutely impaired with resultant urinary suppression, the hazard of hyperkalemia is well recognized. Conditions exist in pregnancy which are conducive to an abrupt development of the hyperkalemic syndrome in the oliguric phase of acute renal failure. The dissolution of decidua and placental-site tissue following delivery or the destruction of erythrocytes in areas of concealed hemorrhage in severe premature placental separation represent extra sources of endogenous potassium. It thus may be anticipated that the pregnant patient with acute renal failure may develop potassium intoxication more readily than the nonpregnant individual. This poses the question whether hyperkalemia with resultant functional cardiac disintegration is the mechanism of death in some of the fatal cases of acute renal failure in pregnancy.

The patient's status with respect to potassium metabolism in the cases comprising this report has been followed by serum potassium determinations and serial electrocardiograms. The relative importance of the electrocardiogram in diagnosing states of potassium depletion or hyperkalemia must be



clearly understood (Fig. 1). While the electrocardiographic changes do not faithfully reflect the potassium depletion state and may, indeed, not appear until severe hypokalemia has been attained, the presence of marked changes, particularly with a compatible history, are strongly suggestive of depletion of body potassium. On the other hand, the electrocardiographic changes which occur during the syndrome of spontaneous potassium intoxication are much more characteristic and more consistently associated with the clinical syndrome. In neither hypo- nor hyperkalemia do the electrocardiographic alterations accurately parallel the changes in the serum potassium. In the latter instance, however, with few exceptions, they are indicative of the syndrome when the clinical picture is present. Inasmuch as it is the disruption of normal cardiac conduction which causes death, the electrocardiographic changes constitute a delicate and important diagnostic and prognostic sign.

#### TYPICAL ELECTROCARDIOGRAPHIC CHANGES IN HYPO AND HYPERKALEMIA

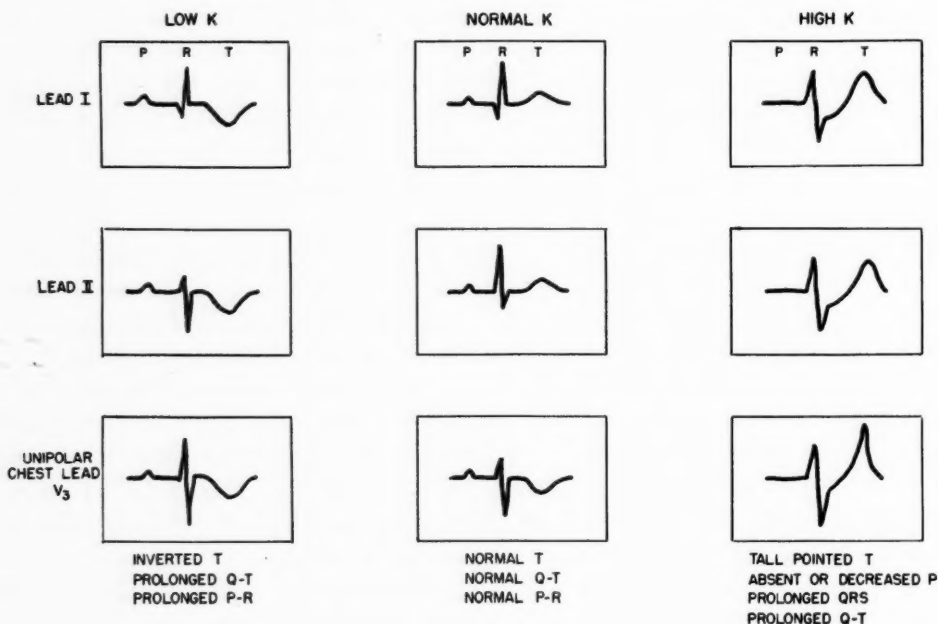


Fig. 1.—Compares significant electrocardiographic changes compatible with hypo- and hyperkalemia to the normal tracing.

It should be stressed that in both syndromes the clinical state may be influenced by factors other than the concentration of potassium in the extracellular fluid. Some of these factors are the serum pH, the concentration of sodium in the extracellular fluid, and in the final analysis, in all probability, the ratio of intracellular to extracellular potassium concentrations. The electrocardiogram provides a composite picture of these changes and in hyperkalemia it reflects the severity of the clinical syndrome.<sup>9, 10</sup> The ease and rapidity of utilization of this laboratory aid has obvious practical advantages.

### Material

Four patients are presented, one of whom had hypokalemia. Three had hyperkalemia. The former was a patient with severe dehydration caused by hyperemesis gravidarum. Hyperkalemia developed in a patient with convulsive toxemia and shock, another with severe toxic separation of the normally implanted placenta, and the final patient exhibited hemorrhage from postcesarean uterine atony.

### Presentation of Cases

#### CASE 1.—Hyperemesis gravidarum.

E. W., aged 29 years, gravida iv, para iii, was referred for hospital care during the eleventh week of pregnancy with a diagnosis of hyperemesis gravidarum. Her history revealed six weeks of ptyalism, nausea, and intractable vomiting. She had been confined to bed in the four weeks prior to admission during which time she had lost 22 pounds. Her diet had been limited to liquids, i.e., tea, broth, and water totaling 800 c.c. daily.

The past medical and surgical history was entirely negative and noncontributory. Her obstetrical history involved three normal term pregnancies without appreciable early trimester nausea or vomiting.

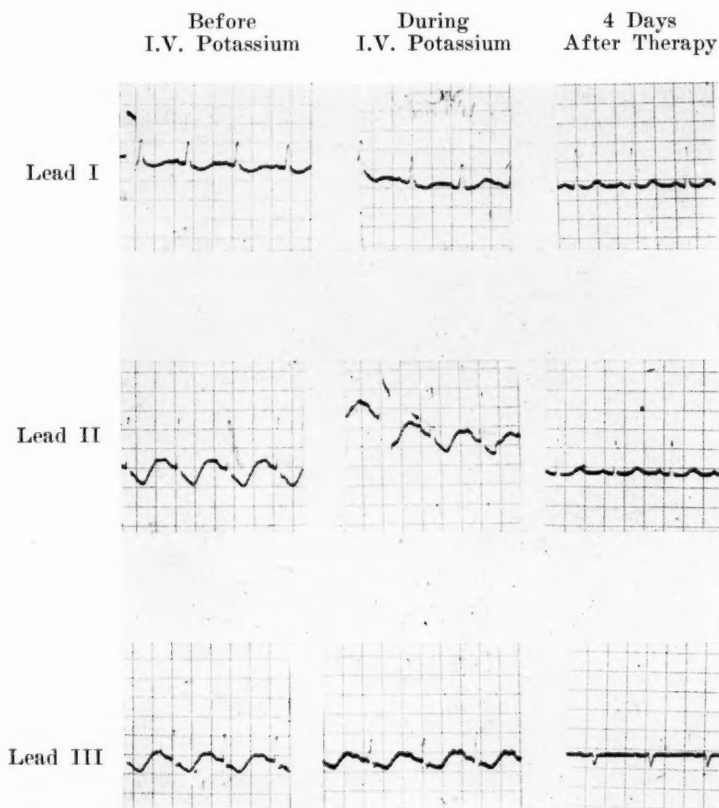


Fig. 2.—Hyperemesis gravidarum. Electrocardiographic changes compatible with hypokalemia. Note particularly the inverted T waves and the prolonged Q-T segment most strikingly seen in Lead II. Note the reversion of these changes following potassium repletion.

Physical examination on admission revealed an acutely ill, dehydrated woman with evidence of some weight loss. There were no important positive findings involving any of the organ systems. In particular there was no emaciation, icterus, vitamin deficiency,

or neurologic disturbance. The urine specimen on admission contained 4 plus acetone and was otherwise negative. Peripheral venous blood was drawn for chemical studies and at the same time intravenous fluids were started to replace fluid losses. The fluids consisted of 2,000 c.c. of 5 per cent glucose in water followed by 1,000 c.c. of 5 per cent glucose in saline. Approximately 6 hours later, toward the end of the infusion, the patient's condition seemed worse. For the first time she complained of extreme weakness while exhibiting moderate dyspnea and difficulty in elevating all the extremities above the bed level. On the following day, respirations were labored, the pulse rapid, and the generalized muscular weakness more marked. Therapeutic interruption of the pregnancy was considered in view of further deterioration of the patient.

The blood drawn on admission proved to contain 2.9 meq. per liter of potassium. In view of this finding and the persistent distressing myasthenia, an electrocardiogram was taken (Fig. 2). It revealed depression of the S-T segment with sinus tachycardia. The decision was made to administer potassium intravenously and in the event the patient's condition continued to decline to terminate the pregnancy.

The improvement that followed was dramatic and gratifying. There was an obvious increase in muscular strength and the movements of the arms and legs were more easily performed. However, the tachycardia and ECG alterations consistent with hypokalemia persisted. In spite of replacement therapy, the serum potassium concentration fell to 2.0 meq. per liter. Potassium chloride was given intravenously over the next forty-eight hours. Following such therapy, the pulse rate slowed and the electrocardiogram assumed a normal pattern, the extremities were freely movable with strong elbow flexion and a good hand grip. Neurological and ophthalmological examination remained normal throughout. With hydration the hematocrit values decreased from 51 to 33 volumes per cent, while serum potassium was 4.3 meq. per liter.

In the subsequent week the patient ate well and responded with a 5 pound weight gain. She appeared normal in every respect and well adjusted to her pregnancy. She was discharged from the hospital for further prenatal care with a diagnosis of severe hyperemesis gravidarum associated with hypokalemia. Her course thereafter remained uneventful and she was delivered normally at term of a healthy infant.

*Comment.*—On admission the patient was given intravenous fluid at a time when the serum potassium concentration was low and when she was undoubtedly depleted of potassium. The fluid, however, was potassium free. During the period of administration, renal losses of potassium continued, and these may have been actually increased by the administration of saline. The infusion of glucose solution results in a drop in serum potassium as glycogen is laid down in cells carrying potassium with it. In addition, the administration of sodium solution, particularly when rapidly infused, is a specific antagonist for potassium effects in the hyperkalemic syndrome. It is thus to be expected that, in hypokalemia, potassium antagonism might result in further manifestations of the hypokalemic syndrome. Indeed, this appeared to be the case for, following this parenteral therapy, the hypokalemic syndrome became strikingly manifest with marked hypotonia, weakness, and dyspnea. This result reveals the dangers of rehydration without adequate evaluation of the state of potassium balance and the necessity for adding this ion to replacement solutions.

CASE 2.—Convulsive toxemia with hemorrhage and shock.

Y. R., aged 29 years, gravida i, para i, was referred because of postpartum anuria. From her history it appeared that the pregnancy had been normal and uneventful until the thirty-second gestational week. Her course then became complicated by the insidious onset of edema involving ankles, hands, and face. She was hospitalized locally the

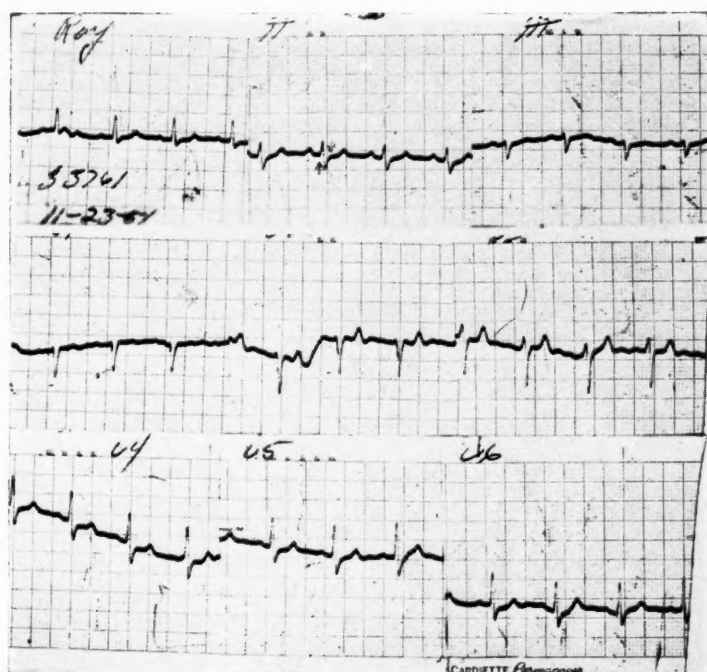


Fig. 3.—Post eclamptic renal insufficiency, Nov. 23, 1951. This tracing was taken only 24 hours before death. It shows very little in the way of ECG change suggestive of potassium intoxication. Precaution should be observed, however, in the interpretation of the small amplitude of the T waves since the T waves particularly in  $V_2$  and  $V_3$  are symmetrical or "tent shaped," and these, even with low amplitude, may signify impending hyperkalemia.

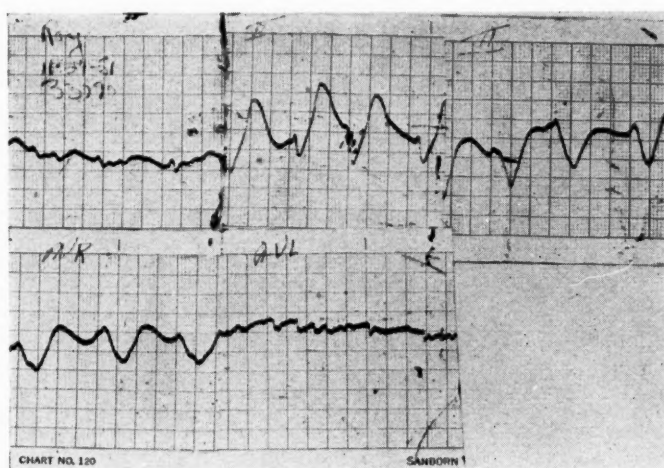


Fig. 4.—Post eclamptic renal insufficiency, Nov. 24, 1951, prior to death. This tracing taken only 8 hours after the one in Fig. 3 shows striking changes of far-advanced hyperkalemia in which the QRS complex has been spread and the merging of the broad T wave and the wide QRS complex resembles the so-called "sine-wave complex" which is characteristic of the terminal phase of potassium intoxication and represents disintegration of the conduction system of the heart.



following week when she exhibited a blood pressure of 210 systolic and 120 diastolic, associated with intermittent vomiting. Three days after admission, she became oliguric and, despite a conservative regimen of fluid and salt restriction, the condition persisted. Induction of labor by amniotomy was performed successfully and spontaneous pelvic delivery occurred in the thirty-third gestational week. The delivery was complicated by postpartum hemorrhage. However, from the record it was not clear whether the hemorrhage was severe or not, and exactly what therapeutic measures were instituted. The puerperium was complicated by many convulsions, vomiting, and a progressive decline in urinary output.

She was admitted to the Peter Bent Brigham Hospital on the second postpartum day. Physical examination revealed an acutely ill, edematous woman, but with no evidence of pulmonary edema. The heart sounds were not remarkable. The remainder of the physical findings except for the edema were not noteworthy. Admission blood chemistry determinations revealed a blood urea nitrogen of 126 mg., sodium 139 meq. per liter, potassium 6.0, calcium 4.0. The initial electrocardiogram was normal. The blood potassium rose slowly to 6.4 meq. per liter, then to 7.0 meq. per liter. Two days after admission, the peripheral reflexes were somewhat diminished and the electrocardiogram showed changes consistent with early hyperkalemia (Fig. 3). Dialysis with the artificial kidney was considered at this time. However, because of the potential dangers of heparinization in a recent postpartum patient with eclampsia, it was deferred. Subsequent developments made this decision difficult to justify. Within a matter of two hours the patient developed marked gross arrhythmia and electrocardiographic disintegration characteristic of advanced hyperkalemia. She died in approximately 40 minutes on the fifth postpartum day (Fig. 4).

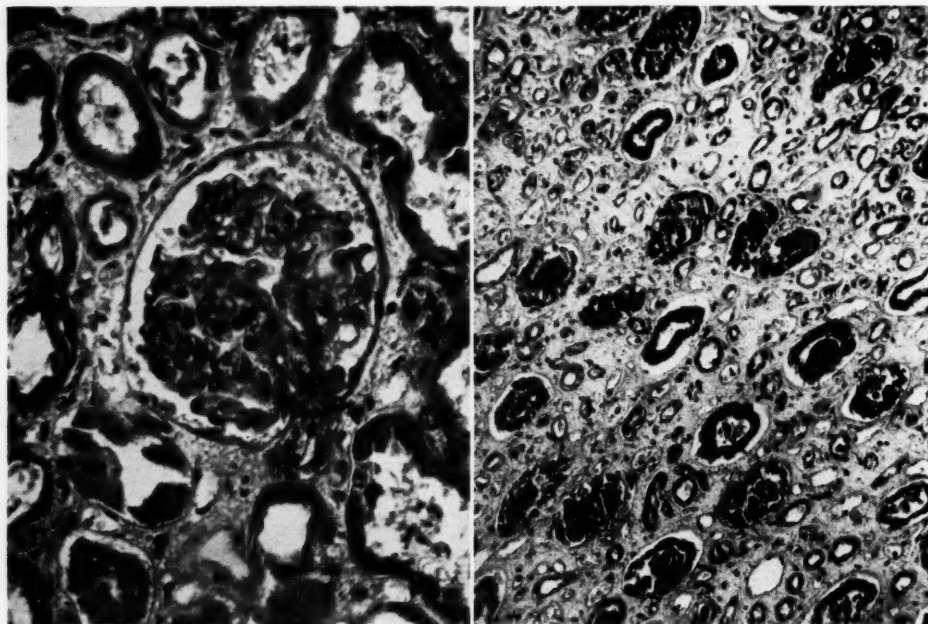


Fig. 5.—The high- and lower-power views of a representative area from the kidney slides of Case 2. The glomerular changes and the tubular epithelial alterations suggest damage responsible for transient renal failure. If potassium intoxication had not intervened, then morphologic recovery seems conceivable.

*Comment.*—The obstetrical sequence involved an acute toxemia, postpartum hemorrhage, and convulsions with anuria. Histologic examination of the

kidney showed the glomeruli to be normal except for suggestive thickening of the basement membrane. Heme casts were present in the lumen of the tubules while the lining epithelium showed scattered areas of necrosis, consistent with a variable picture of acute tubular necrosis (lower nephron nephrosis). These findings are consistent with acute renal failure from an ischemic episode caused by postpartum hemorrhage (Fig. 5). While this patient's kidneys were subjected to a profound disturbance they might have recovered except for the unusually rapid accumulation of serum potassium which caused cardiac arrest.

CASE 3.—Toxic separation of the placenta.

M. O., aged 22, gravida ii, para ii, was referred for admission because of postpartum anuria. Her prenatal course was complicated by vaginal staining in the mid-trimester and by rapid, excessive weight gain. She exhibited leg, facial, and eyelid edema during the twenty-ninth gestational week. Shortly thereafter, she had an episode of vaginal bleeding followed by the spontaneous premature onset of labor. When admitted to her local hospital, the blood pressure was 176 systolic, 120 diastolic. She had evidence of generalized anasarca and the urine contained 3.6 Gm. per cent of albumin. Her labor was uneventful and she was delivered of a premature stillborn infant. In the three days following delivery, her daily urinary output totaled 100, 250, and 25 c.c., respectively.

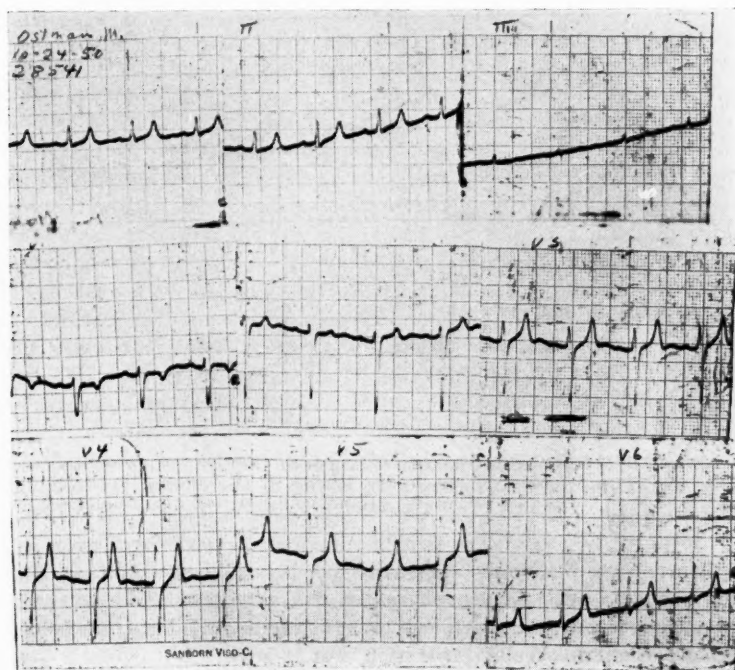


Fig. 6.—Hyperkalemia, predialysis. Electrocardiogram showing evidence of potassium intoxication in the tall peaked T waves particularly marked in Leads V<sub>3</sub>, V<sub>4</sub>, and V<sub>5</sub>.

Concurrently, the blood nonprotein nitrogen rose from 52 to 99 mg. per cent, and the patient became drowsy and lethargic. She was transferred to the Peter Bent Brigham Hospital on the fourth postpartum day. Initially, she complained of marked generalized weakness, lethargy, blurring of vision, and a sense of abdominal fullness. The peripheral reflexes were diffusely reduced. The electrocardiogram revealed changes suggestive of hyperkalemia. However, her clinical condition appeared fairly stable and it was elected

to follow her carefully. The blood urea nitrogen advanced to 137 mg. per cent in the next three days, while the chlorides fell to 83 meq. per liter. Furthermore, on the morning of the fourth hospital day, the seventh postpartum day, she complained of generalized numbness. The electrocardiogram showed disturbing signs of progressive hyperkalemia (Fig. 6).

It was decided to dialyze this patient's blood promptly with the artificial kidney. The blood potassium just prior to dialysis proved to be 9.4 meq. per liter. An excellent chemical response was obtained during the procedure, and the electrocardiogram reverted to normal (Fig. 7). Even more striking was the marked clinical improvement characterized by return of mental alertness, deep tendon reflexes, and the disappearance of the generalized numbness. Following dialysis, the blood urea nitrogen was 81 mg. per cent, chlorides 103 meq. per liter, sodium 140 meq. per liter, and potassium 5.0 meq. per liter.

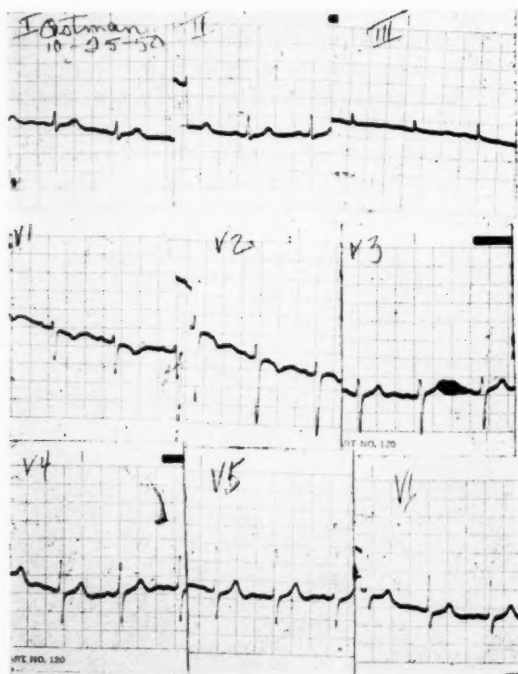


Fig. 7.—Normal tracing during dialysis. Compare the amplitude of the T waves in  $V_3$ ,  $V_4$ , and  $V_5$  with the preceding figure, the improvement in the electrocardiogram is due to removal of potassium and correction of other predisposing metabolic abnormalities by dialysis with the artificial kidney.

The oliguria persisted through four additional days followed by a rapidly accelerating diuresis which reached a peak urinary excretion of 5,500 c.c. on the nineteenth postpartum day. Despite adequate output, the blood urea nitrogen failed to fall below 80 mg. per cent and the phenolsulfonphthalein excretion test revealed 5 per cent dye excreted in two hours. The patient was seen at a two-month follow-up visit at which time the blood pressure was 110 systolic, 80 diastolic. Blood chemistry determinations revealed: blood urea nitrogen 17 mg. per cent, nonprotein nitrogen 21 mg. per cent, sodium 135 and potassium 4.4 meq. per liter. The phenolsulfonphthalein excretion was 55 per cent dye excreted in two hours, while the urine was concentrated to 1.024.

*Comment.*—The events in this case involve premature separation of the placenta, toxemia, and intrauterine death. The postpartum period was marked by progressive urinary suppression, presumably from the renal ischemia caused

by the shock associated with premature separation of the placenta. Despite the anuria, the patient's general condition was satisfactory and renal recovery was anticipated. Instead, acute hyperpotassemia intervened, and it was decided to institute immediate dialysis with the artificial kidney. Although the patient was fully heparinized, no bleeding was encountered from the recently postpartum uterus. An excellent response to dialysis was obtained and the patient made a satisfactory recovery. The clinical course was consistent with acute renal failure resulting from acute tubular necrosis. The oliguric, diuretic, and final recovery phases ideally are to be correlated with intervals of severe tubular damage, regeneration of the tubular epithelium, with return of nephron function, respectively. Again the tendency toward early acute potassium intoxication in this instance, abetted by the hemolysis resulting from concealed hemorrhage, is to be noted.

CASE 4.—Hemorrhagic shock.

J. B., aged 35 years, gravida vi, para vi, was admitted because of anuria following cesarean section. During the thirty-eighth week of pregnancy, she was admitted to her community hospital because of vaginal bleeding associated with undulating lower abdominal pain. Her blood pressure had been normal throughout the prenatal course and the urine was protein free. Except that her second pregnancy involved a 40 pound weight gain and transient proteinuria, the past obstetrical history revealed four uneventful term pregnancies. The fifth pregnancy was terminated by cesarean section for premature placental separation.

In view of the history of previous cesarean section, she was delivered by repeat abdominal hysterotomy on the day following admission. This procedure was completed under spinal anesthesia. It is not clear as to the type of hysterotomy performed or the response in contractility of the uterus. However, the patient lapsed into shock on the operating table, and was given transfusions totaling 1,700 c.c. of compatible blood. The total urinary output on the first postoperative day was less than 200 c.c., and by the third postpartum day there was complete anuria.

Upon admission to the artificial kidney unit at the Peter Bent Brigham Hospital, initial blood chemistry determinations revealed blood urea nitrogen 79 mg. per cent, serum sodium 114, potassium 9.5, and chlorides 86 meq. per liter, and carbon dioxide content 18.4 volumes per cent. The electrocardiogram revealed slight elevation in the T waves and a low R wave consistent with hyperkalemia. A conservative regimen was outlined and, following an intravenous infusion of hypertonic sugar plus insulin, transient improvement was noted. However, three days later the blood urea nitrogen was elevated to 93, and the patient appeared progressively weaker, unable to move the extremities, and it was noted that her voice periodically sank to a whisper. The electrocardiogram revealed characteristic criteria of potassium intoxication.

The patient's blood was dialyzed without incident. Upon completion of the renal dialysis run, the electrocardiogram showed complete reversion to normal. The blood potassium was 6.0 meq. per liter and the blood urea nitrogen reverted to 32 mg. per cent. She exhibited striking clinical improvement which was not maintained and generalized weakness and apathy returned. It was postulated that the failure to show progressive improvement was related to pituitary-adrenal inadequacy, combined with functional impairment of the tubules. ACTH was therefore administered and clinical improvement noted. The serum potassium concentration which had slowly risen to 8.3 meq. promptly reverted to 6.9 meq. per liter.

*Comment.*—This patient demonstrates the consequences of excessive blood loss and shock with resultant acute renal failure. Presumably the renal lesions



were those of severe tubular damage with necrosis of some of the nephrons. The case represents further the particular hazards of blood loss in the obstetrical patient. Although the patient is a likely candidate for Sheehan's disease, at the present time there is no evidence of endocrine dysfunction. The favorable response to ACTH therapy in the puerperium, however, suggests strongly that damage to the anterior lobe of the hypophysis may have occurred.

### General Comment

An accurate biochemical appraisal of the patient in disease has recently been extended to include the aberrations in potassium balance. The recent elaborations of the role of potassium in the body physiology represent extensions of observations made decades ago. Within the framework of our present knowledge, the obstetrical patient under certain circumstances is particularly susceptible to alterations in potassium metabolism.

The production of hypokalemia involves a sequence of prolonged vomiting, dehydration, and starvation, or abnormal losses of electrolytes by the kidney. Hyperemesis gravidarum represents such a syndrome to an extreme degree.

The fact that hypokalemia may develop on occasion with severe hyperemesis is not surprising, since potassium is actually lost in large amounts in gastric vomitus.<sup>11</sup> The detection of potassium depletion supports further the soundness of the concept that the immediate problem of the management of hyperemesis gravidarum is the correction of the metabolic and nutritional disturbances.<sup>12, 13</sup> Indeed, in the past, sudden death has been observed in patients with severe hyperemesis gravidarum following apparent adequate hydration and some clinical improvement. In retrospect it is conjectural whether hypokalemia and resultant respiratory failure may have been the basis for these deaths. Actually this is a reversible state but, if undiagnosed, death from respiratory paralysis may intervene following a severe hypokalemic state.

It is entirely possible that treatment of the hypokalemic state with potassium-free solutions including glucose and sodium may cause the serum potassium to drop acutely as well as aggravate the effects of its depletion. Furthermore, in these instances, the therapy may contribute to the death of patients with hyperemesis following rehydration. It should be stressed that potassium depletion itself, unlike hyperkalemia, rarely requires drastic and immediate potassium therapy. Indeed, if it is possible, the optimum method of replacement is with potassium-containing fluids and food by mouth. Since this is frequently not possible in the severely ill patient, the source and the extent of potassium losses should be considered before large amounts of potassium-free solution are given by vein. If renal function is normal and the serum potassium normal or low, particularly if the electrocardiogram shows evidence of potassium depletion, potassium should be added to the intravenous fluid in a concentration of 20 to 40 meq. per liter.

The specific etiology of hyperemesis gravidarum remains to be determined despite the number of theories that have been proffered which include psychic,

hormonal, and metabolic disturbances. While environmental conditions may arouse emotional conflicts which may accentuate the vomiting, we believe the condition is not primarily of psychogenic origin. The vomiting associated with hysteria is an exception, but the history and symptoms which characterize this disease readily establish the diagnosis.<sup>14</sup> Regardless, the bold fact stands out that the vomiting of pregnancy irrespective of etiological factors may persist to a point where the patient may die from the effects of starvation and electrolyte loss.

In pregnancy, hyperkalemia as a complication of acute renal failure has certain noteworthy features. Nonpregnant patients with acute renal failure will tolerate anuria remarkably well in the absence of infection, severe trauma, and if the circulation is not overloaded with unnecessary fluid. Hyperkalemia may be postponed or prevented in these individuals provided adequate non-protein calories are supplied to minimize protein catabolism. On the other hand, the impression is gained that, in pregnancy, potassium intoxication may develop earlier in the presence of acute renal failure. The thesis is advanced that the regressing placental site and decidua provide the pregnant woman with a singular source for tissue breakdown products, with liberation of excessive amounts of potassium. This tendency toward hyperkalemia is further augmented in premature separation of the placenta with disintegration of erythrocytes from retroplacental hemorrhage. Hyperkalemia in pregnancy may appear in the first rather than the second week of the oliguric phase of acute renal failure. It seems essential that a search be made for the development of hyperkalemia in anuria of pregnancy by the third or fourth postpartum day. The taking of daily electrocardiograms is a useful method of detecting potassium imbalances. It may be concluded that the obstetrical patient with acute renal failure may be a candidate for earlier dialysis if her serum potassium levels are uncontrolled by conservative management.<sup>15, 16</sup>

### Conclusions

1. Hypo- and hyperkalemia are encountered in pregnancy and serious consequences may eventuate if these aberrations in potassium metabolism are not recognized and corrected.
2. Hypokalemia was detected in patients with severe hyperemesis gravidarum; the resultant symptoms responded dramatically to potassium replacement.
3. The suggestion is offered that in patients with severe or marked forms of hyperemesis gravidarum the status of the potassium metabolism be carefully evaluated.
4. When death occurs in hyperemesis gravidarum the question is raised whether it might be caused by respiratory failure, the result of potassium depletion.
5. Hyperkalemia was encountered in three cases with various complications of pregnancy associated with acute renal failure. In all cases, a hypotensive episode was believed to be the basis for the renal changes.

6. Hyperkalemia as a complication of acute renal failure is believed to develop more rapidly in the pregnant than in the nonpregnant patient. The involuting placental site and decidua are regarded as additional sources for the release of potassium.

7. The unpredictable tendency toward rapid potassium accumulation may warrant transfer of the obstetrical patient with acute renal failure to a medical center where earlier dialysis with the artificial kidney may be performed when indicated.

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## IMPLICATIONS OF NUTRITION IN THE LIFE CYCLE OF WOMAN

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*"... one must be concerned not only with the likes and dislikes of the sick person in regard to nutrition but also with the requirements peculiar to his condition." Editorial.<sup>15</sup>*

THE spectacular experimental results involving nutrition frequently have been exploited by charlatans and used ruthlessly to the detriment of human welfare. Demonstrations revealing close interrelationships among nutrients, internal secretions, and metabolism emphasize that nutritional diseases may be chronic or acute, and may develop suddenly or insidiously. Symptomatic presentation of malnutrition, alone or in conjunction with other illness, requires medical evaluation and treatment; prevention of chronic nutritional inadequacy demands public health measures supported by the efforts of physicians, nutritionists, biochemists, physiologists, and all persons involved in the production and processing of food. Education and improved medical care can be expected to lower continually the incidence of severe nutritional disturbance developing from imposition upon a poorly nourished body, stresses arising from accident, illness, growth, adolescence, pregnancy, or aging. This knowledge accentuates the importance of supplying all individuals with ample amounts of all nutrients, in proper proportions, with appropriate medical guidance and care. Especially is this true during the reproductive lifetime of women, for investigators warn of health problems that may arise in later life from detrimental metabolic disturbances in utero.

The individuals who give preconceptional and prenatal medical care have a great responsibility, not only to protect the immediate and future health of the woman, but also to protect the child to be born from any metabolic imbalances and deficiencies, the residual effects of which might constitute systemic or teratologic scars which would plague the future health of that individual and of his descendants. Because an individual appears normal does not mean that all is well nutritionally in his cells, organs, and other tissues, or even in the body as a whole. At a conference on Normal and Pathological Physiology of Pregnancy, discussing Warkany's experimental studies on nutrition in pregnancy, Eastman<sup>51</sup> stated: "As an embryologist sits in his laboratory and studies abortuses, he will naturally find that a large number of them are defective. . . . the implication in the past has been too much that these defective abortuses are usually genetic in character and that the bad product of conception was foreordained at the moment conception



took place. Is the evidence not accumulating that many of the defective abortuses may be due to environmental lack of some kind or another, perhaps thyroid lack, perhaps other hormonal lack, perhaps dietary lack, etc.?"

### Malnutrition in the United States

In the United States, where food is produced in abundance, surveys show that one-half to two-thirds of the population is underfed or poorly fed.<sup>54</sup> Investigators in Canada<sup>29</sup> found the mother to be the most poorly fed member of the family, inasmuch as she often reduces her intake to give the food to other members of the family. Food is necessary for health and well-being at all times throughout life, but dietary quality and quantity have special significance when the body is subject to the augmented physiologic activities of growth, reproduction, or recovery following injury or disease. In prescribing dietaries, therefore, attention must be given to the kinds and amounts of protein, to the proportions of different minerals and to the presence of adequate, but not excessive amounts of specific vitamins. Adequate dietary intake cannot be left to appetite or to the vendors of proprietary synthetic mixtures.

Obesity, a form of malnutrition due to overeating, to consumption of an unbalanced diet, or to other causes, is recognized as a national problem in the United States. The obese woman or the woman who gains excessively during pregnancy is destined to increased susceptibility to disease and probably a shortened life.

There is reason to believe that in this country many adolescent girls and mothers are getting less than 50 per cent of the essential nutrients necessary for optimal health<sup>50</sup>; that racial and socioeconomic influences<sup>28, 66</sup> are plaguing a large proportion of the peoples of the world; that biochemical, nutritional, and pathologic studies focused upon cells, organs, and tissue systems, as well as upon the organism as a whole, will detect nutritional deficiencies at the source; that study of lives (not disease) by the use of "life-time" records, accurately and periodically charted, will reveal to what extent environmental factors and health disturbances will restrain physiologic processes during subsequent epochs of life; that registries for abortuses with carefully documented historical, morphological, and histological records will permit more satisfactory evaluation of the proportionate influences of environmental and genetic factors.

Nutritional deficiencies render adolescents susceptible to diseases such as tuberculosis.<sup>31</sup> In girls, the adolescent period usually includes the years just preceding pregnancy and several years after pediatric care has been concluded. The importance of preconceptional stores of various nutritional factors and of the nutritive stress of adolescent adaptation must be recognized to avoid deficiency states in subsequent pregnancy and to assure that gestation and organogenesis develop the maximum inherent potentiality. Today, as in the lifetime of Professor Lafayette B. Mendel, it is true that "the science of nutrition is in the midst of a continual evolution of facts and development of truth. For the present, therefore, we should 'first get the facts.'"

### Nutrition: In Retrospect

Hippocrates propounded the view that all natural food nourished the body by virtue of containing a single nutrient principle, or "aliment," a term which still is used to designate a nonspecific chemical compound that is employed by the body for the production of energy and may, in addition, be used for growth and repair. In the eighteenth century a rapid succession of discoveries led to a better understanding of food composition and its function in nourishing the body (carbon dioxide by Black in 1757; hydrogen by Cavendish in 1766; nitrogen by Rutherford in 1772; oxygen by Priestly in 1774; the animal calorimeter by Crawford in 1779; and the composition of water by Cavendish in 1786). In 1833, however, William Beaumont, the U. S. Army surgeon who pioneered studies of gastric digestion, still retained this ancient doctrine of a "universal nutrient" in food. It took Lavoisier, the Father of Nutrition, to get all of these isolated discoveries into a complete whole and to explain the process of oxidation and draw the corollary with respiration in the animal body which led to the concept that "life is a chemical function."

The intervening times have been rich in discoveries which have led to the energy concept of foods and the evaluation of different foods on the basis of their chemical and biological properties. The biological method of food analysis, which is the basic tool of the science of nutrition, was initiated by Magendie (1783-1855). Coincidentally, William Prout (1785-1850), the English physician who discovered "free" hydrochloric acid in gastric juice in 1823, propounded the modern theory that food must furnish not only one, but many kinds of nutrient substances. Beyond the "proximate principles"—protein, fat, carbohydrate, and minerals—today more than 50 nutrients obtained from foodstuffs are known to be present in the body and necessary for life and health. A recent publication<sup>58</sup> quantitates milk in terms of more than 250 different constituents.

### Nutrition: A World-Wide Problem

Nutrition is a twentieth-century science. Within the lifetime of the great physician whom this volume honors, nutrition has been established as a recognized science and applied on a world-wide basis. Because World War II demonstrated the importance of nutrition to the health of troops and population groups everywhere and placed modern evaluation of food on a *cost per nutrient* basis, i.e., efficient food production and utilization in terms of nutrient yield rather than volume as market value. The United Nations economic policies with regard to food supply<sup>67</sup> are now being related not so much in terms of dollars and cents as in terms of satisfying the *physiologic needs* of the common man. World food supplies and nutritional "targets" now are considered in terms of a balanced diet, with food, agriculture, and nutrition as basic factors in international relations.

Food is basic in the complex of our modern civilization but it took a global war to make the world conscious of the importance of food supply in the conservation of human life.<sup>54</sup> Special agencies of the United Nations are working

on international cooperation in this field.<sup>19</sup> The Food and Agriculture Organization (FAO), the first of these, was created in 1945 with 44 nations agreeing after intensive surveys that: (a) two-thirds of the world's people are undernourished, (b) their health could be vastly improved if they were able to get enough of the right kind of food, (c) the farmers of the world could produce enough if they used the best agricultural methods, (d) full-time work for all could be provided by increased production and efficient distribution. The World Health Organization (WHO), created shortly thereafter with the objective of attainment by all peoples of the highest possible level of health, set new horizons in its constitution: (a) health is a state of complete physical, mental, and social well-being and not merely absence of disease or infirmity, (b) the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition, (c) healthy development of the child is of basic importance; the ability to live harmoniously in a changing total environment is essential to such development. The United Nations International Children's Emergency Fund (UNICEF) in work with mothers and children has stressed the rehabilitation of children and adolescents of countries which were the victims of aggression and has supplied food for these vulnerable groups.

### **The Frontier of Human Welfare**

Concepts of the composition and role of foods have changed with the rapid development of the science of nutrition—considered by Lusk<sup>33</sup> as a study of the food substances and biological processes which utilize them in the body, and by Mendel<sup>43</sup> as “The Chemistry of Life.” Nutrition is recognized as the prime factor in the propagation of individuals with the maximum potential for physical development and in their maintenance of the best physical status possible throughout life. It has been demonstrated that physical state, nutrition, and health depend upon the quality of food and that it is equally important to satisfy hidden hunger and hollow hunger.<sup>54</sup> The ultimate goal of the science of nutrition is to provide a standard of dietary intake that will allow amply for the health and well-being of the human race.

Maternity, as Adair<sup>1</sup> said, certainly is “the frontier of human welfare.” Pregnancy introduces many complex problems because the fetal organism is living symbiotically within the mother and is dependent upon her body for the proper execution of its own more or less independent physiologic processes. Prolonged use of submarginal diets may force a body into a suboptimal nutritional state. Depressed nutritional state may develop during fetal life, infancy, childhood, adolescence, or adulthood. Infants and children recover rapidly with improved dietary intake, but the adolescent body tends to resist reconditioning procedures with the result that return to health is delayed. After an inadequate dietary intake of long duration in one or all epochs of life prior to childbearing, the maternal body at conception faces not only enlarged nutritional requirements for avid fetal needs and expanded metabolism for maternal physiologic growth but also the repletion of deficient nutritive stores.

### Dietary Recommendations Versus Dietary Requirements

The Food and Nutrition Board of the National Research Council was organized at the outset of World War II. The tentative *Recommended Daily Dietary Allowances* adopted by the Board in May, 1941, represented the combined judgment of more than 50 persons qualified to express an opinion. As more extensive and exact data became available, revisions followed in 1942, 1944, and 1948.<sup>49</sup> The revision of 1953, now in press, has been made available by the Food and Nutrition Board for reproduction here (Table I).

In using the Allowances, it is important to remember the general principle followed by the Board, namely, that the quantitative levels are sufficiently liberal to be "suitable for maintenance of good nutritional status." The recommendations represent levels of nutrient intakes which are considered normally desirable goals or objectives; "they are not called requirements because they are not intended to represent merely literal (minimal) requirements of average individuals, but levels enough higher to cover substantially the individual variations in the requirements of normal people." Thus, the recommended amounts are generally higher than average requirements but generally lower than the doses used to meet needs created by pathologic states, or in compensating for an earlier period of depletion.

No two people are alike in nutritive background and requirements. Some persons have unusually high requirements for one or more nutrients. Consequently an individual might ingest a diet which provided the recommended allowances and still have a nutritional deficiency. If such a woman becomes pregnant, the allowances may be insufficient and disrupt the growth of the embryo. Darby<sup>51</sup> pointed out that there are possibly two mechanisms to be considered: "The nutrition of the fetus depends, first, upon the nutrients in the mother's diet, and secondly, upon the nutrients which are passed on from the mother to the fetus. If by any chance a mother were well nourished and yet the process of transference of a nutrient to the fetus were defective . . . it would be possible for the fetus to experience a nutritional deficiency despite a perfectly well-nourished mother. . . . It is conceivable too, considering the nutritional levels at which these mother animals must exist in order to produce defective young and the clinical experience which we have had at Vanderbilt, that if fetal nutrition does play a role in the production of congenital malformations in the human, it may be through the indirect process rather than through the direct process. That is to say that the mechanism is defective transfer of nutrients, not a grossly deficient maternal diet."

Recognition was given to the strategic relationship between mother and child when the National Research Council, Food and Nutrition Board appointed a Committee on Maternal and Child Feeding and charged it with the responsibility "to implement improved health of the nation through better coordination of scientific advances in the field of pediatrics and obstetrics." Several interpretative reviews of the scientific literature resulted.<sup>38, 66</sup>



TABLE I. FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL, RECOMMENDED DAILY DIETARY ALLOWANCES, REVISED 1953  
DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY WOMEN IN THE U.S.A.  
(ALLOWANCES ARE CONSIDERED TO APPLY TO PERSONS NORMALLY VIGOROUS AND LIVING IN TEMPERATE CLIMATE)

	AGE (YEARS)	WEIGHT		HEIGHT		CALORIES	PROTEIN (GM.)	CALCIUM (GM.)	IRON (MG.)	VITAMIN A I.U.	THIAMINE (MG.)	RIBO- FLAVIN (MG.)	NIACIN (MG.)	ASCOR- BIC ACID (MG.)	VITAMIN D I.U.
		(KG.)	(LB.)	(CM.)	(IN.)										
Women	25	55	121	157	62	2,300*	55	0.8	12	5,000	1.2	1.4	12	70	
	45	55	121	157	62	2,100	55	0.8	12	5,000	1.1	1.4	11	70	
	65	55	121	157	62	1,800	55	0.8	12	5,000	1.0	1.4	10	70	
Pregnant (third trimester)						Add 400	80	1.5	15	6,000	1.5	2.0	15	100	400
Lactating (850 ml. daily)						Add 1,000	100	2.0	15	8,000	1.5	2.5	15	150	400

\*These calorie recommendations apply to the degree of activity for the reference woman. For the urban "white-collar" worker they are probably excessive. In any case, the calorie allowance must be adjusted to the actual needs of the individual as required to achieve and maintain her desirable weight.

### Nutritive Intake

The increasing demand for expanded information and the discrepancies among existing tables of food composition continue to handicap physicians and other investigators participating in nutrition research. Even in the United States which abounds in many kinds and varieties of foods, the latest compilation of the composition of foods<sup>69</sup> was published by the Department of Agriculture in 1950 and provides values for 15 nutrients in 751 foods. Standard tables of food composition are based upon analytic values for the nutrients in foods, which are subject to all variations and errors involved in the analyses. Although the determinations and calculations may be accurate, the values still are subject to wide variations in the composition of foods and the losses incurred in processing and preparation for consumption. Thus, food composition tables merely serve as guideposts. In many problems, it is important to compare chemical determinations of dietary intake with calculated values merely to know within what range the calculated values may safely be judged reliable. This knowledge is especially important in planning therapeutic diets, or diets for vulnerable groups such as adolescent girls and childbearing women. In nursing mothers, for instance, a variation of 200 to 500 calories per day in the estimation of a marginal diet may, over a period of time, mean the difference between success and failure in satisfying nutritive needs of the baby, and in the maintenance of the maternal body weight.

In a consideration of the uses and abuses of dietary study methods, we<sup>28</sup> stated: "The estimation of the nutritive values of food eaten is one of the many important phases in the evaluation of nutritional status. Dietary intake, however, must not be confused with nutritional status. No matter how much one learns about dietary nutrients in the food, all one can estimate is dietary intake and the investigator cannot from such data alone determine nutritive status, which also involves the condition of the person who consumes the food. However, an estimation of dietary intake is essential in any interpretation of measurements of nutritional status, which also have limitations, but a better assessment of dietary intake contributes to more precise evaluation of nutritional status."

Dieckmann<sup>51</sup> stated: "... in order to make a sound recommendation, we need to know considerably more about what constitutes a sufficient diet, to what extent deviations affect significant laboratory and clinical findings, the extent to which the nutritional needs are being met prior to dietetic instruction, and the time and effort required to effectively change food habits. In this area alone, much needs to be done to study effective educational procedures and methods for measuring results. . . . What constitutes a sufficient diet will be determined best by a pooling of the results of many laboratories. . . ."

Various methods have been used to evaluate the physiologic adaptation of individual women to the increased nutritional requirement of reproduction.<sup>66</sup> Some insight into the metabolism of mother and fetus is gained by chemical analyses of fetuses.<sup>32</sup> Metabolic balance studies have contributed direct measure-

ments of the utilization of materials from foods. Amounts of nutrients retained usually exceed the requirements of the fetus, and many mothers find themselves physically more fit after than before pregnancy.

If a mother enters maternity in a nutritionally unstable state, her metabolic response may be quite different from that of the well-nourished individual. Fig. 1 demonstrates differences in protein and calcium utilization from adequate diets by two pregnant women, one of whom had been malnourished from childhood.<sup>26</sup> The influence of nutritive state and physiologic conditions other than gravidity upon maternal storage in pregnancy is illustrated by conspicuous differences in total accumulation of nitrogen and calcium by two women of contrasting nutritional background. Uninterrupted metabolic balance studies reveal significant variations among individuals under similar circumstances. In using the metabolic balance method for determining food requirements, maternal nutritive state and physiologic constitution must be taken into consideration when interpreting dietary requirements for reproduction.

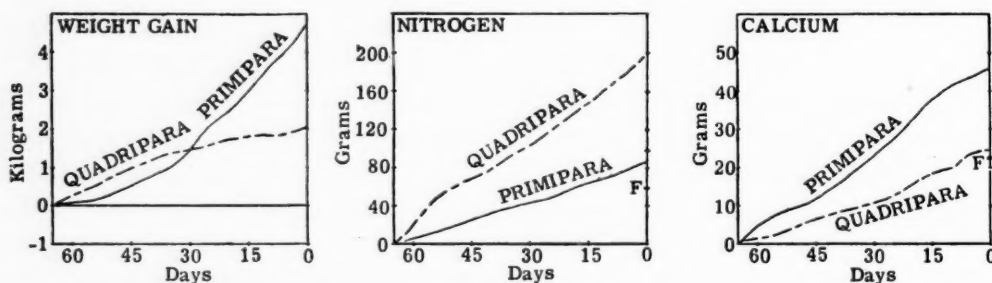


Fig. 1.—Conditioned malnutrition. Weight change and nitrogen and calcium utilization during pregnancy. The quadripara was a well-nourished individual but the primipara had been malnourished from childhood. *F* indicates the level of fetal storage.

Evidence indicates that both dietary intake and physiologic state of the mother may be directly reflected in the retention and utilization of nutrients during pregnancy and in the general nutritive state of the gravid woman.<sup>11</sup> Maternal physiologic responsibility does not terminate with parturition, however, but proceeds in an even more intense degree during lactation. To interpret metabolic findings during the progression of lactation it is important to know what chemical events have taken place with regard to the course of labor, delivery, and parturition, and subsequently the quantity and quality of the milk she secretes.<sup>25-27</sup>

There is a dearth of precise information on food eaten by nursing women who are successfully feeding their babies and at the same time preserving their own body tissues, and maintaining buoyant health. Records of food consumption have been kept during the lying-in period, but seldom have they been continued after this period.<sup>17</sup> The mammary secretion of a healthy mother is generally acknowledged to possess nutritive qualities which provide advantages for her infant, although the factors responsible for its superior value have not been defined clearly.<sup>38</sup>

In women, the physiologic processes motivated by lactation are accompanied by increased requirements for minerals and other food essentials.<sup>17, 58</sup> The find-

ing of significant losses of calcium during the period of intensive milk flow, despite a calcium intake seemingly adequate to maintain bodily function with a rich surplus to accommodate the added demands of milk production, and addition of vitamin supplements to the dietary, points to the need for more thorough knowledge of the physiologic processes involved in reproduction. As yet an actual quantitative measure of the nutritive factors essential for the preparation and protection of the maternal organism during childbearing remains undefined.

### Malnutrition

Optimum nutrition no longer is construed in the narrow meaning "absence of obvious disease" but expresses broader and more positive attributes such as stamina, efficiency, reserves, and capacity. Food must nourish the body under all types of conditions and circumstances. Chemical, physiologic, and physical research applied in studies of life processes has demonstrated the dynamic nature of the body, and we have learned indeed that nutrition is truly *food in action*. The term "malnutrition" has been used too loosely—frequently to cloak ignorance. Malnutrition is a general term which indicates nutritional failure varying in severity over a wide range. It may indicate only slightly inferior nutritional status produced by a shortage or excess of one or more of the requirements of good nutrition: the right foods in ample amounts at the proper time, adequate rest and exercise, and favorable environment.

Malnutrition may occur also in the presence of dietary adequacy. If a nutritional deficiency arises from an inadequate (or excessive) diet, it is a *primary* deficiency. If it is caused by factors other than an inadequate diet, it is a conditioned, or *secondary* deficiency. Conditioned deficiencies are caused by factors that interfere with the ingestion, absorption, or utilization of essential nutrients or by factors that increase the requirement for them, destroy them in the body, or cause them to be excreted. For example, pregnancy may be a conditioning factor and cause malnutrition by interfering with the ingestion of food, or by increasing nutritive requirements.

In general, malnutrition involving conditioned or secondary deficiencies as a result of disturbances of body function and as the sequelae of disease, together with the gross manifestations of malnutrition recognized as deficiency diseases, is an acute medical problem which calls for therapy based on individual diagnosis. In such cases, the physician must evaluate the role of nutrition and other factors involved, determine whether the deficiency is "cause" or "symptom," and prescribe the treatment indicated. With some cases, secondary deficiencies can be treated simultaneously with primary therapy; in other cases, application of results of nutrition research must await control of disease or dysfunction; in still other cases, the therapy necessary to bring an illness under control may cause, or aggravate, a nutritional disturbance. The public health aspect of nutrition, in so far as it involves "prevention," is concerned with averting nutritional failure, thus eliminating the cause of primary deficiencies and reducing the causes of conditioned or secondary deficiencies. In this objective, the approach is to malnutrition as the result of underfeeding or misfeeding, or both.



Underfeeding consists of eating inadequate amounts of food. Poverty is the greatest contributor to underfeeding, commonly designated as "hunger" or "hollow hunger." It is obvious that underfeeding is necessarily misfeeding.

Misfeeding is a much larger problem than underfeeding. With sufficient food to allay hunger, the diet still may not be adequate in meeting the chemical needs of the body. Further, even with a diet adequate in all respects, physiologic factors may prevent proper use of the food materials by the body. The consequences of misfeeding are frequently designated as "hidden hunger." Lack of education and indifference are major factors in misfeeding. Misfeeding also results from failure to make special provision for increased needs for certain nutrients during periods of stress in the life cycle or under conditions which make more stringent demands upon the food eaten.

Misfeeding may continue for months, even years, without producing deficiency disease or any specific symptom of dietary failure. The clinical evidence of nutritional failure may consist only of deterioration of the teeth, headaches, mild gastrointestinal upsets, or other such vague complaints. In other instances misfeeding may occur over short or long intervals without causing complaint by the individual. With children especially, chronic misfeeding which may date from birth frequently results in the body becoming "conditioned" to a poor diet. While such bodies do not make a physiologic protest against the lack of proper nourishment, the results are demonstrated by poor nutritional status. There is no doubt that poor nutrition over extended periods in childhood produces an adult of inferior physique, less stamina and resistance to disease, and the prospect of premature aging. Indeed, Hippocrates<sup>22</sup> (460-370 B.C.) recognized so long ago that "a slender and restricted diet is always dangerous in chronic diseases, and also in acute diseases, where it is not requisite. And again, a diet brought to the extreme point of attenuation is dangerous; and repletion, when in the extreme, is also dangerous."

### Nutritional Status

Physicians and investigators respect more fully than ever before the role of imbalance and dietary relationships in nutrition;<sup>16</sup> the vital importance of the interrelationships among all essential nutriment in the diet;<sup>20</sup> of the metabolic function of the placenta;<sup>68</sup> and of the maternal-fetal nutritional relationships.<sup>60</sup> It is paramount to extend the scope of knowledge beyond gross observations such as body weight change, reproduction outcome, or even metabolic balances if the physiologic processes of reproduction are to be fully understood. Investigation in these fields needs the concerted efforts of specialists in such diverse phases of medicine and science as obstetrics, nuclear physics, pediatrics, hematology, enzymology, anatomy, endocrinology, internal medicine, ophthalmology, nutrition, biology, and psychology.

Every individual has a characteristic physiologic capacity to utilize and store chemical elements from ingested foodstuffs predetermined by heredity, eating and elimination habits, physical and mental states. Chemical fluctuations are evident among children of the same age, body size, and living under the same environmental conditions, who were observed for successive months<sup>35</sup> and among pregnant and lactating women.<sup>25-27</sup>

The distribution of nutrients in the human body varies from one organ to another, depending upon the kind and intensity of metabolic activity required. The placenta seems to serve as a little-understood governing device between the progression and egression of nutrients between mother and fetus.<sup>39, 47</sup> The growth of the placenta and fetus do not parallel one another; however, the ratio of the fetal weight to the placental weight at the seventh month of pregnancy is about 3.7:1, while at term it increases to 7.5:1.<sup>70</sup>

Studies on the metabolism of slices of the human placenta *in vitro*, aged six weeks to term, show that in all the metabolic functions tested, the placenta at term is considerably less active than the placenta in the first half of gestation.<sup>68</sup> As the gravid state progresses, there is an increase in the solid fraction of the placenta, a decrease in oxygen consumption to about half the rate earlier, a marked decrease in the initial glycogen content, a loss of the ability to synthesize glycogen, a decrease in the rate of glucose utilization, a loss of the ability to produce glucose, and a slight decrease in the rate of pyruvate utilization and lactate production, thus providing a biochemical basis for the concept that the placenta is less active metabolically at term than earlier in pregnancy. Vitamins are essential in the enzyme systems of carbohydrate and energy metabolism of the placenta; thus in its functional and nutritive role of initiating and servicing the fetal organism, emphasis is given to the need for adequate dietary and metabolic control in the initial stages of pregnancy in order for the fetal organism to develop its maximum inherent capacities.

Using long-term nitrogen and calcium balances and growth measurements in studies of adolescent girls, Johnston<sup>31</sup> is exploring the thesis that the increase in tuberculosis among young girls may be due to a failure to meet nutritional requirements peculiar to the growth demand at that time. He believes his work shows a correlation between adequate nitrogen storage and the course of the infection.

Generally, the belief is that diets of human beings are seldom as extremely deficient as those used in experimental animals to produce noteworthy, reproducible defects in embryos. True, diets with a *single deficiency* are unlikely to occur in unrestricted human beings; however, cumulative scientific evidence indicates that if deficiencies are encountered in population groups they are usually *multiple* in character, of long duration, and cumulative in intensity since dietary habits, family customs, and socioeconomic conditions are not readily changed. Border lines between health and disturbed physical state and the relative importance of genetic and nutritional factors are being studied intensively.

Attention also is being given to the various forms of stress and the manner in which the body adapts itself to them.<sup>18, 46, 57</sup> Protein metabolism is altered following an injury of any sort, such as burns, fractures, delivery, puerperium,<sup>26, 27</sup> and surgery.<sup>40</sup> The period of increased destruction or catabolism of protein follows the injury and the more severe the stress, the greater are the intensity and duration of the catabolic phase.<sup>27, 35, 37, 40</sup> The period of recovery is characterized by the rebuilding of body stores when anabolism exceeds catabolism. After mild stress, loss of protein may be observed for only a few days, whereas, after excess stress, it may occur for several days or weeks.

At the inception of a disturbed physiologic or pathologic state, the regulatory mechanisms of the body are thrown out of balance. The results may be observable in the level or distribution of blood components, in the level or distribution of urinary excretion, in the retention of nutrients from the food intake and in the change in composition or structure of the blood cells, and of their function.<sup>66</sup> Electrophoretic observations of levels of total serum protein, albumin, and alpha<sub>1</sub>, alpha<sub>2</sub>, beta, phi, and gamma globulins,<sup>7, 37</sup> during pregnancy and following delivery, demonstrated a characteristic pattern of distribution of these components in uncomplicated pregnancy. In some complications of pregnancy, the serum protein distribution was altered and patterns characteristic of the complications were obtained.<sup>34</sup>

In evaluating the nutritional states of large groups of mothers and their newborn babies, methods combining determinations of blood concentration levels (hemoglobin, total protein, vitamin C, vitamin A, carotene, thiamine, riboflavin, and alkaline phosphatase) with evaluation of dietary intake and clinical examinations were used.<sup>9</sup> Seriatim data representing the physiologic course of successful human reproduction were collected in this laboratory.<sup>39, 47</sup> Determination of six blood components gave evidence of definite physiologic adjustment with resultant change in blood levels shortly after conception and throughout reproduction which differed according to dietary intake, socioeconomic and racial factors. Fig. 2 portrays the medians and ranges of the concentrations in the blood of white private patients (of H. C. M.) who composed the highest economic group and in the blood of their infants. Levels of each blood component followed different trends. Concentrations of some blood components changed appreciably shortly after conception; others later, in the third trimester. Differences between the average values for components of the blood of the mothers and their infants demonstrated the adjustments brought into play in maintaining homeostasis in the maternal and fetal bodies. The placenta appears to conserve hemoglobin and vitamin C for fetal construction, function, and reserves, for these components were appreciably more concentrated in the newborn infants' blood than in the mothers' blood. The average levels of total serum protein, carotene, and vitamin A in the infants' blood were less than those of their respective mothers' blood.

One investigator<sup>23</sup> clearly states the facts: "Under some circumstances the nutritional status of an animal determines what will happen with a given genetic background. Conversely the genetic background determines what will happen with a given nutritional status." The nutritional requirements of an individual depend upon nutritional status, age, sex, activity, metabolic function, and nutritive reserves. The plane of nutrition of an individual may determine the extent to which certain elements are retained or rejected by the body. The underfed individual will tend to store large amounts of nutrients when the diet is improved, while the malnourished or diseased individual with conditioned deficiencies actually may be inhibited from using certain materials until chemical adjustments have taken place within the tissues to such a degree as to permit retention.

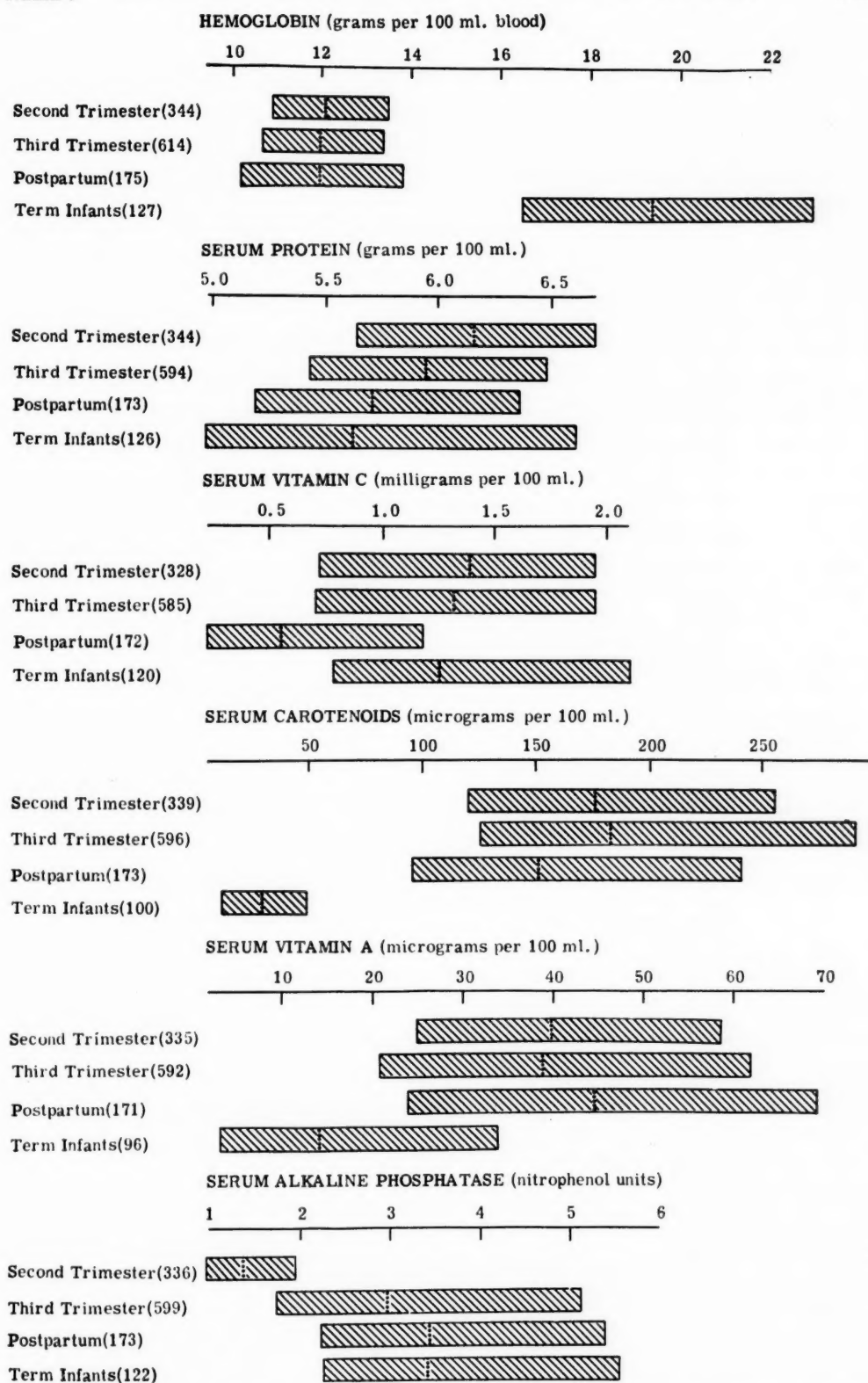


Fig. 2.—Medians and ranges of concentrations of six components in the blood of white patients during pregnancy and 1 to 9 days post partum, and of their infants when 1 to 8 days old. Numbers of samples are given in parentheses.



### Physiologic Growth: Preconceptional and Prenatal Nutrition

In an interpretative review of the literature on maternal and child health,<sup>66</sup> it was pointed out that the so-called "physiologic growth" of women, which continues after the characteristic body weight and length of the individuals have been attained, ceases only with the termination of the reproductive period of life. During menstruation, pregnancy, lactation and postpartum reparative periods, metabolic processes present nutritional requirements which correspond closely to those of growth in size. All of these physical states increase the body's need for various nutritional factors, and the requirements for some food components may be increased more than those for others.

The preconceptional period, in which the body develops its potential for childbearing, also must be considered a segment of the reproductive cycle and a factor of major importance in relation to maternal and infant nutrition. The stores of some nutritional factors in the mother organism prior to pregnancy have been shown to be of great importance to the future health of mother and child. If pregnancy occurs during the years of adolescence when the maternal organism itself is developing, the maternal body must continue to fulfill the nutritional requirements for its own growth and development and meet those of the fetus concurrently. The health of teen-agers takes on great importance.<sup>45</sup>

It is difficult to make detailed observations of human beings under conditions that regulate their existence and environment beyond a few months—a brief period in the life span. Knowledge is being gained in identifying and evaluating developmental changes which take place as the individual grows and matures by observing normal individuals under consistent environmental conditions, using simultaneously a battery of chemical, physical, and nutritional status tests. The most impelling problem today resides in the discovery of the relatedness to one another of the various available tests and the development of new ones. The recording of successive data from coordinated procedures carefully executed, meticulously recorded, capably interpreted, and clearly presented in life-time records<sup>8</sup> (infancy, childhood, adolescence, reproductive period, and senescence) will lead to quantitative measurement of the changes taking place.

The obstacles hampering attainment of clear, concise, and nonconflicting terminology are increased by the gaps in our knowledge of actual occurrence within living cells, organs, tissues, and the organism as a whole. To illustrate, in a consideration of natal-day deaths Bundesen<sup>5</sup> pointed out that prematurity is actually a measure of length of uterogestation, although by definition adopted by the American Academy of Pediatrics<sup>2</sup> and the World Health Organization<sup>19</sup> it is a weight of 5 pounds, 8 ounces, and under. He stated: "We cannot logically remain content to let infants die of a word, instead of finding the true causes of death, and then trying to eliminate these causes. . . . We realize that to make a more successful attack on natal-day deaths requires the combined experience and knowledge of those in many fields of medical and scientific endeavors. Through a full interchange of ideas and a pooling of

combined knowledge and experience of those interested in many allied fields, more effective plans might be developed which will represent the best present-day thoughts and knowledge in these scientific fields. . . . Those responsible for this failure to reduce early infant mortality include health officers, obstetricians, pediatricians, hospital administrators, and most emphatically includes the role played by the pregnant woman herself as well as all others concerned with the care of the pregnant woman and her newborn infant."

The progressive gains in maternal body weight during pregnancy are only a gross measurement of nourishment because this as well as other growth increments are known to vary in chemical composition. Accumulation of body weight is not a direct measure of storage of tissue-building constituents. Nonetheless, weight gain is important in relation to pregravid weight, to rate of loss or gain in the first and second trimesters; to total gain during gestation; and to gain or loss subsequent to delivery, in the puerperium and during lactation. Excessive weight gains or losses increase the susceptibility of the mother to disease and the health hazard of the infant during the first year of life.

That many women fail to seek medical advice within the first trimester of pregnancy is well known. Tompkins<sup>65</sup> pointed out the delicate balance that exists in the pattern of gain throughout pregnancy: "An approximately normal gain in weight during the first two trimesters is necessary to preclude the hazard of toxemia; and an excessive restriction in the rate of gain during this period seriously increases the probability of premature labor. A failure to gain at a normal rate during the first two trimesters must not be compensated for during the latter part of the second trimester in an attempt to avoid premature labor. Such a procedure then moves the patient directly into the zone of increased probability of toxemia, and the incidence of severe preeclampsia and eclampsia increases almost proportionately to the rate of gain during this period. . . . The pattern of premature labor is established by an initial underweight status of a patient and/or her failure to gain at an acceptable rate during the first two trimesters." Further: "If maximum protection is to be obtained for each individual patient, every effort must be made to establish an adequate nutrient intake sufficient for her needs both qualitatively and quantitatively as early in pregnancy as is possible, and maintained at this critical level throughout the duration of the individual pregnancy concerned. Any deviation of even previously considered minimal degrees, particularly in the patient of lowered nutritional adequacy, markedly increases her probabilities of either premature labor or preeclampsia." These findings are in general agreement with those established by Dieckmann.<sup>12</sup>

Although prematurity is generally considered a pediatric problem, it would seem to be a better index of prenatal physiology or pathology. In so far as malformations are concerned, with organogenesis completed in embryos within the initial twelve weeks following conception and the placenta having reached full maturity, delayed medical and nutritional care beyond the first or second trimester would have little chance of erasing the effects of the destructive forces prevailing during this time. The increased dietary require-

ment for vitamins and other nutrients during reproduction is established during the early physiologic adaptation to the gravid state and it has not been sufficiently emphasized that the time of meeting the nutrient needs in relation to the advancement of pregnancy may be of great importance to the health of the infant and mother.

### Infant Health and Maternal Nutrition

Recent summaries of the literature emphasize an intimate interrelationship between nutritional status of mothers before and during pregnancy and the health of the children they bear.<sup>6, 23, 66</sup> Eating the right kinds and amounts of food is reflected in better maternal health during gestation, in less trauma from the stress of labor and delivery, and in speedier recovery; and in better preparation for nursing the infant. The fact that the infant at birth is nutritionally nine months old is proof sufficient that special consideration should be given to the diet of the mother during gestation. Reciprocal relationships exist between fetus, child, adolescent girl, and mother.<sup>36</sup>

Modern biological research, using tracer substances for studying metabolic pathways, has demonstrated that the body is in a dynamic state of flux and that there are no static or completely isolated compartments in the living body. The whole maternal-child unit may be affected; the structure or function of one organ may be altered without others being obviously influenced. With each successive addition of facts, the theories about the parasitic existence of the fetus are being altered and clarified.

Relationships have been demonstrated between the prenatal diet of mothers and development of rickets in the infants.<sup>13, 41, 55</sup> When mineral and vitamin intakes are low and mineral metabolism is defective during pregnancy, not only are the results a predisposition to bone and tooth defects in the fetus, but also the associated nutritional disturbances in the mother may be one of the etiological factors in vomiting, eclampsia, osteomalacia, and premature labor.<sup>66</sup> An overstrain on the function of hematogenesis is shown by the mild secondary anemia which is common in pregnancy, and in some instances becomes severe. The blood requirements of the fetus, the increased maternal blood volume, the blood loss during parturition, and other factors in this anemia may, in turn, contribute to the metabolic overloads.

Newborn infants of mothers with hypochromic anemia may show a normal blood picture, but develop anemia during the first year of life. If iron is given to the mother during pregnancy, this anemia is averted. Apparently the fetus of an iron-deficient mother does not accumulate enough of this essential blood component to carry it through infancy unless the supply of the element in the mother's body is ample. Stevenson, Worcester, and Rice<sup>62</sup> found that a considerable portion of the mothers of malformed children were anemic.

Child research institutes, concentrating upon observations of mothers during pregnancy and at delivery and of the growth and development of infants, are providing the proof that a campaign for better nutrition of chil-

dren should have its inauguration with mothers during preconceptional and pre-natal periods. Sontag,<sup>61</sup> from physical, biochemical, and dietary observations of women during pregnancy and post partum, together with periodic studies of the children from birth to maturity, stated: "Roentgen examination of a group of newborn infants has shown that the severity of round bone scars resulting from the birth process is very much greater in those children born of mothers whose diets were *grossly* defective in the muscle- and gland-building elements and in vitamins. This fact suggests that children from inadequately nourished mothers may suffer a greater neonatal growth interruption than will those of well-nourished mothers."

It behooves the obstetrician, pediatrician, embryologist, physiologist, biochemist, and psychologist to pool efforts to find out which of the various kinds of causes that may produce defective human embryos are operative most commonly, and which have operated in specific individual cases. Practically all malformations in human beings are believed to be determined before the eighth to the twelfth week of embryonic life, at which time organogenesis is nearing completion. Incidences of malformations may occur in mothers who may or may not have been ill in the first trimester.<sup>21, 51, 62</sup> Many women have not visited a doctor at this time and those who have had medical advice may or may not have shown observable clinical signs of deficiency or abnormality.

#### Timing Factor in Teratology

Thirty years ago, Stockard<sup>63</sup> emphasized the importance of timing in experimental teratology. To date, experimental modification of pig, rat, guinea pig, and chick embryos has been produced as the direct consequence of inadequacy of the maternal diet in one or more of thirteen different nutrients, namely, vitamin A, vitamin E, ascorbic acid, riboflavin, pantothenic acid, folic acid, biotin, cobalamin (vitamin B<sub>12</sub>), niacin, and tryptophane, iodine, manganese, and copper. There seems to be a specific teratogenic action of any of the vitamin deficiencies.

At an early state of development, frustration of the growth impulse in the fetus may cause, as consequences, widespread degeneration of the skeletal, soft, and nervous tissues culminating in deformities, loss of sight, hearing, and even life itself.<sup>51</sup> Experimental embryologists have studied the way in which the embryonic body is organized. In the discussion of embryonic defects at a conference on normal and pathologic physiology of pregnancy, Corner<sup>51</sup> stated: "The so-called theory of organizers shows us that the development of a normal individual is the result of a chain of events within the embryo. Each developing tissue acts to organize the undifferentiated tissue adjacent to it into new tissues and organs. Thus each step in the development of the body depends upon the completion of a previous step. The chain of events may be interrupted or delayed at any time. No matter whether the harmful agent is a toxin or physical injury or on the other hand the effect of a gene or of some constitutional accident, its interruption of the chain of organization at any given time will produce the same kind of defect."



### Genetic Versus Nutritional Influences

In the past quarter of a century, the conflicts between theories of genetic and nutritional origin of malformations have been partially narrowed and resolved. Investigators have demonstrated in carefully controlled experiments, using numerous species, that developmental processes can be altered by environmental disturbances with a resulting reduction in growth similar to that produced by abnormal genes.<sup>66</sup> Since the vitamins and trace minerals act as components of enzyme or biochemical mechanisms in the body, it is possible for a vitamin deficiency and a defective gene to have identical effects and lead to the same congenital abnormality.<sup>23</sup>

The course of a biochemical reaction may be altered by the destruction of a gene, by x-ray, by alteration in intake of an essential component of the biochemical mechanism of growth by toxic substances (rubella), deficiency of iodine, etc.—causes of widely different nature, yet all frustrating growth if enforced during early gestation when organogenesis is taking place.

In relation to the nutritional state of a pregnant woman, the preconceptional status may be evaluated not only from a genetic but also from a nutritional point of view. A girl who has not completed growth and whose body is not nutritionally provided for could not be expected to develop a nutritionally sound fetus without careful medical supervision throughout pregnancy. An older woman may have depleted her store of food factors. Similarly, a woman whose dietary pattern is habitually poor would become more depleted with each succeeding pregnancy and lactation period. Thus, familial tendencies in pathologic conditions may not necessarily be genetic, but may result from poor food habits of long duration.

Food habits are not easily changed, especially in those of low economic status and in the disinterested groups. Abnormalities resulting from many types of interruptions of growth may be revealed by autopsy and histological examinations when general clinical inspection reveals no external symptoms. Similarly, biochemical abnormalities and pathologic conditions exist to varying degrees without outward symptoms. The incidence of malformations of the central nervous system increased in German children during World War II; this was ascribed by some<sup>14</sup> to maternal malnutrition, with resulting prenatal pathology of varying severity. Because of the susceptibility of the central nervous system in its formative period, it does not seem too farfetched to question whether fetal anoxia at birth, with consequent cerebral damage in some cases, may not be due to debilitated intrauterine breathing responses, devitalization of the biochemical mechanism in oxygenation of the blood, too rapid placental senescence, as well as to inability to withstand effects of anesthesia, anoxia, and shock.

Basic studies of body chemistry will disclose new approaches in research. They will clarify the *modus vivendi* of the symbiotic existence of mother and fetus and enlarge our knowledge of the co-enzymes derived from vitamins and their role in enzymatic and biochemical reactions which occur in the utilization of amino acids, inorganic constituents, other metabolites, and vitamins by the bodies of both mother and fetus.

Should we not look more closely into the possibility that prenatal malnutrition may contribute to the increase in mentally retarded and physically crippled children which might be in large measure preventable? In reflecting upon the art and science of medicine, a recent writer<sup>14</sup> emphasized that "some clinical problems can be solved by knowledge, some by experience, and some by understanding. The application of these three qualities has come to be known as clinical instinct or clinical wisdom." We need more wisdom on the far-reaching effects of malnutrition upon health from the level of the cell to the adult organism. We cannot retreat from exploring the immense possibilities of nutritional science in attaining optimum health and in treating disease.

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## ETIOLOGICAL ASPECTS IN THE PROBLEM OF TOXEMIA OF PREGNANCY

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**D**ESPITE the many investigations carried out to determine the cause of toxemia of pregnancy, this has not yet been found. In my opinion, however, it probably will be before long.

To find the cause it is necessary to know exactly what cases are to be classified as toxemia.

We believe the principal symptom of toxemia of pregnancy consists of a rise in blood pressure, both of the systolic and—possibly even more important—of the diastolic pressure. It is frequently stated in the literature that toxemia of pregnancy may occur without hypertension. So far we have never observed such a case among our very large number of patients. Therefore, in our opinion, toxemia of pregnancy may be definitely excluded when there is no rise in blood pressure. This is of great importance in making a differential diagnosis. Various other diseases may also cause convulsions during pregnancy, which might be regarded as eclamptic attacks, if the normal blood pressure did not suggest a different explanation. Thus we have observed eclamptic-like attacks in thrombosis of the cerebral veins, in hemorrhagic encephalitis, and uremia due to sodium chloride deficiency. In all these cases the normal blood pressure, and in the case of the patient with encephalitis the fact that a high systolic pressure was associated with a low diastolic pressure, put us on the right track. Likewise, the seizures of true epilepsy are known to occur more frequently in pregnancy, while, in some cases, this form of epilepsy appears only during pregnancy.

There is no consensus as to the maximum value above which the blood pressure must have risen to permit this condition to be defined as hypertension. Browne<sup>1</sup> puts the upper limit of a normal blood pressure at 120/80, others put it at 140/90, in our clinic we put it at 130/80. It would be very desirable to reach a unanimous opinion with regard to this matter.

The symptom ranking next in importance to hypertension is edema. It is not essential for this condition to be demonstrable by pits in the skin following pressure applied by the fingers. Even in eclampsia this need not be the case. The toxemia may develop at such a rate that the edema does not have time to spread from the deeper layers of tissue to the skin. In that event the development of edema can be determined only by the rapid increase in body weight.



Usually albuminuria has occurred as well. It may be absent, however. I shall discuss the cause of this in greater detail.

A toxemia of pregnancy may terminate in two final stages: the one is eclampsia, the other abruptio placentae. The latter will be particularly liable to occur when the toxemia has developed on the basis of a pre-existent vascular disease. A study of the literature shows that as yet there is no general acceptance of the fact that a premature separation of the placenta usually is a terminal stage of toxemia of pregnancy.

### Etiology

In the study of the *etiology* of toxemia of pregnancy it is essential to determine the conditions under which it may appear. As early as 1925 Beker<sup>2-6</sup> showed that it is most likely to occur in the event of an increased resistance in the blood vessels of the pregnant uterus. We<sup>2</sup> also hold this view. This is the case when, among other conditions, the uterus is stretched tightly around its contents (primiparas, multiple pregnancy, hydramnios) and when the vessels are not sufficiently wide, which may be due either to the fact that the vascular system is hypoplastic or to the appearance of anatomical changes in the vascular wall (arteriosclerosis), preventing adequate dilatation of the vessels. Detailed investigations, carried out in my clinic by Admiraal,<sup>7</sup> showed that toxemia of pregnancy is superimposed upon a (possibly latent) vascular disease in approximately 75 per cent of the cases. The lumen of the artery is not the only factor, however. The incidence of toxemia will also increase when there is a greater amount of placental tissue, as in hydatid mole, multiple pregnancy, and the presence of a large fetus.<sup>8-15</sup>

In view of these facts I have come to regard a relative decrease in the quantity of blood flowing to the placenta as a possible cause of the appearance of toxemia. Thus the same kind of thing might be thought to occur in a placenta with an inadequate supply of blood as in a kidney through which an insufficient quantity of blood flows.<sup>8, 12</sup> After we had started our investigations on this subject, we found that Ogden, Hildebrand, and Page<sup>16</sup> held identical views. To study the effect of a diminished supply of blood to the placenta, experiments have been carried out in the gynecological clinic of the University of Amsterdam, first by Sindram (1943) and later by Mastboom. Initially (1940-1945) only rats were available. These animals were found to be too small for experiments of this type. Therefore further experiments had to be postponed until after the war. For technical reasons the first experiments were so-called acute experiments. In the event of positive results, attempts were to be made to carry out chronic experiments as well.

These experiments were carried out by Mastboom on 8 pregnant dogs; in 6 cases by applying Goldblatt clamps around the uterine arteries, the ovarian arteries having been previously ligated; in 2 cases by applying a clamp to the aorta immediately below the level of the renal arteries. Blood pressure rose in every case (Figs. 1 and 2). In 8 nonpregnant dogs there was no change in blood pressure, with the exception of a slight rise or fall during a few seconds (Fig. 3).

Chronic experiments are far more difficult than acute experiments. When the supply is too markedly diminished, the fetus will die. Reduction of the lumen will result in a rapid increase of the collateral circulation. New experiments are in progress to overcome the difficulties. We have carried out experiments in rats, rabbits, and dogs. An additional difficulty with rats and rabbits consists in the determination of the blood pressure. This cannot be done in the hindlegs or tail, as constriction of the aorta, which appears to be the only method of reducing the blood supply to the uterus in very small animals, also reduces the quantity of blood flowing to these organs.

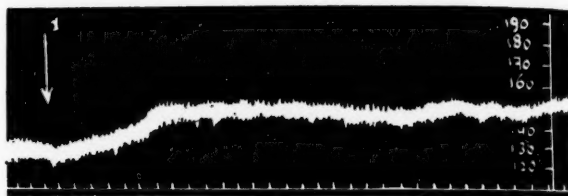


Fig. 1.—Blood pressure of pregnant dog. 1, Partial closure of aorta clamp distal from renal arteries, after ligation of ovarian arteries. Time: 15 seconds.



Fig. 2.—Blood pressure of pregnant dog. 1, Partial closure of clamps around uterine arteries, after ligation of ovarian arteries. Time: 10 seconds.

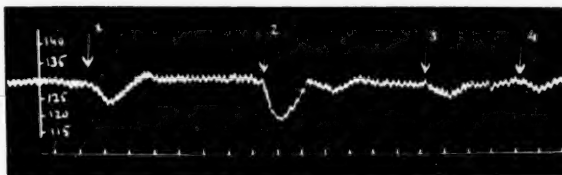


Fig. 3.—Blood pressure of nonpregnant dog. 1 and 3, (Partial) closure of aorta clamp distal from renal arteries, with 2 and 4, opening of aorta clamp. Time: 10 seconds.

The view that the quantity of blood flowing through the intervillous spaces diminishes in toxemia is supported by the results of investigations carried out elsewhere. By means of radioactive sodium Browne and associates<sup>17</sup> were able to show that the blood stream is reduced to approximately one-third; Sauter<sup>18</sup> was able to demonstrate this decrease by hysterotocometry. By means of a Lóránd tocograph Parviainen, Lankinen, and Soiva<sup>19</sup> were able to determine an increased tonus of the uterus in toxemia of pregnancy. Browne and Veall believe the diminished flow of blood to be the result rather than the cause of the toxemia. For they also observed a decrease in pregnant women with hypertension, but not affected with toxemia. From their paper it cannot be concluded what criteria they employ to determine whether toxemia or hypertension without toxemia has occurred. In pregnant women with

essential hypertension the blood pressure frequently decreases in the second trimester. Is it not likely that toxemia must even be said to have occurred when there has been no fall in pressure? In that case something must have happened in the body which prevents the hypotensive hormones produced in the placenta from exerting any action. Browne<sup>20</sup> reports that the children born from his patients with essential hypertension always were alive when the blood pressure fell in the second trimester. I regard this as further evidence of the fact that this is the normal state.

Sodium chloride is also known to play an important part in rises in blood pressure, in the development of edema, and in the appearance of convulsions. This is only the case, however, when the kidney fails to function properly. The condition of the adrenal cortex is another important factor. When substances causing constriction of the arterioles are produced in an ischemic placenta, this will also result in a disturbance of the blood supply in the kidneys and adrenals. This may cause albuminuria and retention of sodium chloride and water. This is verified by the experiments carried out by Chesley, Markowitz, and Wetchler,<sup>21</sup> which showed albuminuria to be due to spasm of the afferent arterioles of the glomeruli. In the unusual case of toxemia of pregnancy without albuminuria it might be that prior to the appearance of the toxemia the blood vessels are wide enough that a certain constriction will still permit sufficient blood to flow through the glomeruli and tubules, to prevent the appearance of pathological changes.

An increase in corticoids, especially mineralocorticoids, in pregnancy with toxemia has been reported in several papers. Mastboom<sup>22-24</sup> has advanced arguments in support of the hypothesis that the increased quantity of mineralocorticoids does not originate from the adrenals. He believes it to be possible that progesterone is produced by reduction from desoxycorticosterone in a normally functioning placenta. In the event of a functional disturbance of the placenta this might occur to a lesser extent, manifesting itself in an increased elimination of mineralocorticoids and a diminished elimination of pregnanediol. This has indeed been observed by various investigators.<sup>22-24</sup>

It is generally agreed that a spasm of the arterioles occurs in the bodies of pregnant women with toxemia. All changes observed at autopsy may be explained by a vascular disturbance (see, among others, Sheehan<sup>25</sup>). The macroscopically and frequently also microscopically observable changes in various organs of the body are even more marked in patients with abruptio placentae. Abruptio placentae as a terminal stage of toxemia of pregnancy occurs mainly in women with chronic, either manifest or latent, vascular disease. Hemorrhages and necroses in and about the uterus (Couvelaire's uteroplacental apoplexy) have been a particularly frequent subject of discussion. Initially, it was often thought that the blood was driven from the retroplacental hematoma into the surrounding tissues. This, however, does not afford an explanation of the fact that the most severe hemorrhages by no means need occur in proximity to the retroplacental hematoma. Nor does this explain why severe hemorrhages may also occur outside the uterus, especially in the parametria. The hemorrhages and necroses which occur in abruptio placentae are most readily

explained by the theory that, owing to the considerable fall in blood pressure resulting from the separation of the placenta, an insufficient quantity of blood is propelled through the arterioles of the body which have been constricted by spasm. The relatively frequent incidence of necrosis of the renal cortex in abruptio placentae may also be explained by this theory. If the cause consists in a sudden fall in blood pressure, then a method of treatment which restores the normal blood pressure by replenishing the lost quantity of blood shortly after abruptio placentae must be able to prevent a Couvelaire uterus as well as severe hemorrhages in other parts of the body and necrosis of the cortex of the kidney. During the period in which I have been in charge (since 1938), only one patient in the gynecological clinic of the University of Amsterdam died of necrosis of the renal cortex following abruptio placentae. This patient had not been given prenatal care at our clinic. As the blood pressure was normal at the time of hospitalization, although the symptoms showed that separation of the placenta had undoubtedly occurred, the assistant on duty did not administer any blood. He did not realize that a patient with premature separation of the placenta must have lost a great quantity of blood and therefore must have had a higher blood pressure prior to the separation. The case was not brought to my attention until about eighteen hours after the separation of the placenta. Nevertheless, blood was still administered. Although the secretion of urine slowly increased, the woman died on the tenth day. At the International Congress on Obstetrics and Gynecology, held in New York in 1950, Sheehan reported that, in patients who had died of anuria following abruptio placentae, he had invariably observed lesions of the kidney which could be attributed to a severe spasm of the arterioles, which, in his opinion, had occurred during or very shortly after the abruptio. He was unable to define the cause of this spasm. In my opinion a spasm always occurs in toxemia, even before the placenta has separated. The sudden fall in blood pressure then results in an ischemia.

There will also be a danger of ischemia with its sequelae in all other cases of vasospasm, especially when changes have occurred in the vascular wall (arteriosclerosis). In these cases one should therefore be extremely careful in taking measures which may result in a fall in blood pressure, such as spinal and caudal anesthesia and abstraction of blood. The fact that a severe fall in blood pressure in toxemia may give rise to a necrosis of the cortex of the kidney is suggested by the course of the disease in the following case report.

A 30-year-old primipara, who had been pregnant for 30 weeks, was hospitalized in the clinic. She was affected with Marfan's disease and showed toxemia of pregnancy with hypertension. Among other things, Marfan's disease is associated with lesions of the heart and vascular system. Especially during pregnancy, this may result in a dissecting aneurysm. The woman suddenly went blind. She complained of severe pain in the cardiac region. Thereupon she was referred to our clinic. She arrived in a state of severe shock. Anuria developed. The last 12 hours prior to death there was no secretion of urine. The bladder was empty. A dissecting aneurysm and a bilateral necrosis of the cortex of the kidney were detected at autopsy.

I have not found any case of necrosis of the renal cortex associated with a dissecting aneurysm in the literature. In my opinion the necrosis of the renal



cortex in this patient must have been due to the fact that a toxemia of pregnancy (spasm of the arterioles) was accompanied by a sudden severe fall in blood pressure.

The incidence of eclampsia showed a marked decrease during the war years, especially in the famine winter. For the obstetrical and gynecological clinic of the University of Amsterdam this is shown in Fig. 4.

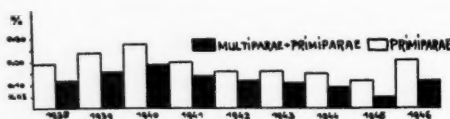


Fig. 4.—Relative frequency of eclampsia at Amsterdam, 1938-1946.

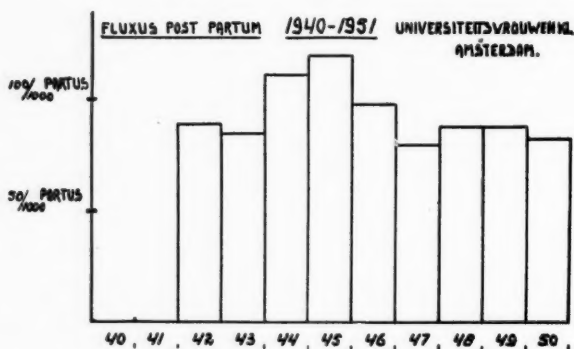


Fig. 5.

During the winter of 1944-1945 the food supplied contained only 500 calories daily. This marked decrease in the incidence of eclampsia probably was due to the poor state of the muscular system caused by malnutrition. The poor condition of the muscles of the arterioles causes a fall in blood pressure.<sup>26</sup> The diminished tonus of the uterine muscle results in a reduced pressure upon the vessels of the uterus, so that more blood can pass through.<sup>8, 15</sup> The effect of malnutrition on the diminished incidence of eclampsia has also been observed by De Snoo and Remmelts.<sup>27</sup> They found the incidence to be far lower in Indonesian women of the poorer classes than in more well-to-do women. Racial influences could be excluded.

Our hypothesis is also supported by the fact that, as the incidence of eclampsia diminished, atonic postpartum hemorrhages became increasingly frequent.<sup>28</sup> The curves showing the incidence of atonic postpartum hemorrhages and eclampsia are inverted images of each other (Figs. 4 and 5).

### Treatment

When toxemia of pregnancy is due to an insufficient supply of blood to the placenta, the logical treatment, both to prevent the appearance of toxemia and to prevent its aggravation, must consist in measures taken to increase the flow of blood in the pregnant uterus. To study this possibility, the omentum was sutured onto the uterus in pregnant rabbits, after the epithelial lining

had been removed by various methods. An increased circulation originating from the omentum was not observed, not even when stasis had been induced in it by the ligation of veins. Proceeding on the assumption that substances that dilate the vessels are produced in a normally functioning placenta, vasodilative agents (such as adenosine triphosphate) were introduced into the wall of the uterus at the site where the omentum had been fastened. No dilatation or appearance of new vessels was observed. For similar reasons Theobald<sup>29</sup> performed a denervation of the internal iliac arteries in three women with essential hypertension, in whom the fetus had died in utero in previous pregnancies. All these women gave birth to living children in their next pregnancies. Before proceeding to a similar operation, we wish first to await further experiences.

Stimulated by papers published by Smith and Smith,<sup>30</sup> we have administered estrogens to many patients with toxemia according to the method suggested by the Smiths, proceeding on the assumption that this would increase the blood supply of the uterus. There were neither drawbacks nor advantages to this treatment. Others, such as Dieckmann,<sup>31</sup> have arrived at a similar conclusion. So far we have not tried any other drugs to improve the flow of blood.

It is also important to know the etiology and to gain an insight into the cause of the frequent fetal deaths in utero. Both intrauterine death and the loss of birth weight in prolonged toxemia may be explained by an insufficient supply of maternal blood to the placenta. Treatment which increases the circulation in the uterus will undoubtedly also improve the prognosis for the child.

### Summary

To study the etiology and the most satisfactory method of treatment, one should always be sure that the case is toxemia of pregnancy. When there is no hypertension, toxemia may definitely be excluded.

Toxemia may result in eclampsia and in abruptio placentae, the latter being most likely to occur when the vessels are arteriosclerotic.

Toxemia of pregnancy probably is due to an insufficient supply of maternal blood to the placenta. Various acute experiments are reported. So far, we have not found the correct method in chronic experiments.

In abruptio placentae, Couvelaire uterus, necrosis and hemorrhages in other parts of the body, as well as necrosis of the cortex of the kidney are due to ischemia, caused by a considerable fall in blood pressure associated with marked constriction of the arterioles.

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## RENAL FUNCTION STUDIES IN THE TOXEMIAS OF PREGNANCY

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FOR several years, considerable emphasis has been placed on the utilization of the various renal function tests in attempts to assist in the diagnosis, treatment, and ultimate classification of the toxemias of late pregnancy. While some of these determinations have been of inestimable value, others have been of no material assistance in reaching any significant conclusion. No single test of renal function has been found which could be considered uniformly characteristic of any one type of toxemia of pregnancy. Despite the fact that practically all the routine evaluations of renal function, either singly or collectively, have been used, no constant correlation can be shown between the laboratory results and the clinical picture found in the toxemias of pregnancy.

Since it is not possible to apply any one test of renal function toward determining the exact status of the toxemia, we undertook a study of several determinations, both routine and research, performed practically simultaneously on patients with toxemia of pregnancy. In order to make a fairly complete evaluation of the renal implications in these patients, 147 patients with the various types of toxemia of pregnancy were studied, with the use of all the commonly employed tests of renal function. These included determination of albuminuria, carbon-dioxide combining power, blood urea nitrogen, dilution test, concentration test, urea clearance test, and the phenolsulfonphthalein test. In addition to these routine studies, fifty patients with toxemia were studied at a research level employing the necessarily more extensive and prolonged methods of determination of renal function. On these latter fifty patients, glomerular filtration rate, renal plasma flow, filtration fraction, and the average renal output in cubic centimeters per minute were determined. Glomerular filtration rates were determined using inulin while renal plasma flow was determined with the use of para-aminohippuric acid, utilizing techniques previously described by us.

### Proteinuria

All patients, on admittance to our service, are catheterized. We feel that the voided specimen in obstetric patients, unless completely negative, is of no practical value. Since the voided specimen in the majority of pregnant women admitted to our service is invariably positive for protein, we feel that the study of catheterized urine is a more desirable routine in order to gain unequivocal information as well as to avoid multiple repetition of urinalyses.



The sequence of events in the development of pregnancy toxemia, as we have observed the condition, occurs as follows: (1) weight gain, (2) demonstrable edema, (3) hypertension, and (4) proteinuria. Proteinuria in the toxemias of pregnancy varies from patient to patient, from day to day, and from hour to hour. Because the absence of proteinuria from one specimen does not necessarily rule out renal disease, the other evidences of pregnancy toxemia must, therefore, indicate further urinalyses. This was evident among our group in that all patients, at some time during their toxemia, showed evidence of proteinuria. Approximately half the patients showed no proteinuria on the admittance specimen, yet on subsequent examinations it was found in all of the patients with pre-eclampsia. When proteinuria is present, it is not necessarily proportionate to the other evidence of toxemia of pregnancy. Since toxemia of pregnancy must be considered essentially as cardiovascular-renal disease, gradations of alterations of any one part of the complex may be present.

It is now generally considered that the proteinuria found in toxemia of pregnancy occurs as a result of vasospasm of the renal arterioles; such spasm generally involves the afferent glomerular arterioles. It is conceivable that, when this happens and even though a marked change in blood pressure may be present, no evidence of proteinuria may exist. However, following the release of such vascular spasm, proteinuria does become evident. Chesley<sup>1</sup> found the filtration of protein in patients with primary renal disease to be fairly constant, but noted that the filtration of protein in toxemia of pregnancy was quite variable. This appears to support the thesis that proteinuria is very likely secondary to vasospastic influences. If proteinuria is present in early pregnancy, we suspect primary renal disease either of a degenerative type due to glomerulotubular nephritis or to chronic pyelonephritis. In our references to pyelonephritis, we refer to the chronic disease and not to the acute infected hydronephrosis so common in otherwise normal pregnancy. Where proteinuria persists in the early postpartum period, we do not feel that one is justified in making a definite final diagnosis as to causation of proteinuria. Our final diagnosis is reserved, for classification purposes, until evaluation is carried out late in the puerperium or well after the completion of puerperal influences. Thus such evaluation for final classification of the patient may not be possible until three to six months following delivery. If, at these times, complete reversal of clinical signs and symptoms has occurred, the condition is considered etiologically as being a true toxemia of pregnancy. If there is sustained evidence of proteinuria at these times, the clinical diagnosis of primary renal disease can justifiably be made and can probably be considered as having existed prior to the pregnancy, particularly if there was evidence of proteinuria early in the pregnancy.

We are reluctant to view proteinuria in pregnant patients as being physiologic until all evidences of renal pathology have been found to be consistently absent. Erythrocytes, leukocytes, and casts are not usually seen in the true toxemias of pregnancy. Where proteinuria is present, it should suggest the presence of these elements and make mandatory the microscopic examination

of the sediment. Albuminuria may well present the first evidence of hematuria or pyuria secondary to primary infectious, traumatic, or neoplastic disease of the genitourinary tract.

### Blood Urea Nitrogen

The normal values of the blood urea nitrogen in the nonpregnant patient are between 10 and 20 mg. per cent. The average value in pregnant patients has been found by us to be considerably lower than in the nonpregnant patient. This has been substantiated by practically all observers, including Dieckmann,<sup>2</sup> Cadden and Faris,<sup>3</sup> and Stander and Cadden.<sup>4</sup> The average value during pregnancy, based on a summary of most authors, is from 8 to 10 mg. per cent. No satisfactory explanation has been proposed for this decreased blood urea nitrogen except the general statement of hemodilution. If this is so, it may indicate the necessity for our reconsidering an acceptable upper limit of normal for pregnancy. In our group of patients (Table I) 153 determinations of the blood urea nitrogen were performed. These were all performed on admittance, prior to treatment. The blood urea nitrogen was found to be within the lower limits of normal in over two-thirds of our cases. With the exception of nine cases, all values were within the accepted limits of normal for nonpregnant individuals. The concentration of the urea nitrogen in the blood, therefore, cannot be considered as evidence indicating a particular type of toxemia of pregnancy. Only 4.5 per cent of all patients classified as having true or acute toxemias of pregnancy had blood urea nitrogen levels above 20 mg. per cent. The blood urea nitrogen was normal in all patients with benign essential hypertension and in one patient with malignant hypertensive disease complicated by pregnancy. In the two patients with chronic pyelonephritis the BUN was significantly elevated.

TABLE I. BLOOD UREA NITROGEN ON ADMISSION (153 CASES)

	1-10 MG. %	11-19 MG. %	20 AND ABOVE MG. %
Mild pre-eclampsia	55	18	3
Severe pre-eclampsia	27	11	2
Eclampsia	1	—	—
Benign essential hypertension	19	5	—
Malignant essential hypertension	5	1	1
Chronic glomerular nephritis	—	1	1
Chronic pyelonephritis	—	—	2
Chronic vascular nephritis	1	—	—
Total	108	36	9

### Carbon-Dioxide Combining Power

The alkali reserve in the normal nonpregnant individual is generally stated to be between 60 and 65 volumes per cent. However, in the normal pregnant individual a slight decrease occurs, the normal levels being reduced to between 50 and 55 volumes per cent. This physiologic decrease is attributed to the increased respiratory rate in pregnancy causing a compensated carbon-dioxide deficit. Dieckmann<sup>5</sup> states that pregnant patients with mild pre-eclampsia and those with essential hypertension have CO<sub>2</sub> levels similar to

those found in normal pregnant patients. As noted in Table II, our analysis of 156 patients reveals results different from those found in normal pregnancy. The majority of our patients showed evidence of acidosis, particularly among the true toxemias of pregnancy. This might well indicate impairment of the excretory mechanism of the kidney or perhaps tissue anoxia in the kidney. This seems to conform to our findings in the study of renal plasma flow in these patients. Such findings have seemed to offer suitable indication for the determination of tubular function as measured by the concentration test and the PSP test. In the hypertensive group, approximately half of our patients showed a rather marked deficit of carbon dioxide, a finding which is not in agreement with that of Weiss, who felt that, among patients with toxemia of pregnancy, a lowering of the carbon-dioxide combining power practically never occurs. Among our patients we found that, even though the patient was classified clinically as having mild pre-eclampsia, laboratory evaluations showed carbon-dioxide combining power levels of as low as 22 volumes per cent, with blood urea nitrogen levels above 30 mg. per cent. While we have found the carbon-dioxide combining power usually to be decreased in pre-eclampsia and eclampsia and that it does offer a valuable guide in the initial management of these patients, we feel that other alterations must be studied in order to classify the type of toxemia clearly.

TABLE II. CARBON-DIOXIDE COMBINING POWER (VOLUME PER CENT ON ADMITTANCE)  
(156 CASES)

	1-39 VOL. %	40-45 VOL. %	46-54 VOL. %	55-60 VOL. %
Mild pre-eclampsia	17	31	19	7
Severe pre-eclampsia	18	11	10	3
Eclampsia	1	—	—	—
Benign essential hypertension	1	10	13	2
Malignant essential hypertension	2	2	3	1
Chronic glomerular nephritis	—	1	1	—
Chronic pyelonephritis	2	—	—	—
Chronic vascular nephritis	1	—	—	—
Total	42	55	46	13

### Concentration Test

Renal function may be succinctly defined as the ability to excrete waste products and solids in water, and thus could not be better expressed than by a measurement of the specific gravity of the urine. While this determination is often one of the last to be performed, it is probably the most important as well as the most sensitive routine measure of renal impairment. It is an adequate method for determining the concentration of the total urinary solids. When urine-concentrating ability is such as to produce a specific gravity of 1.023 or greater, renal function may be considered normal.<sup>2</sup> The distinctly normal kidney can concentrate to 1.029 and 1.032. As noted in Table III, approximately 50 per cent of our toxemia patients showed evidence of renal impairment, as measured by their ability to concentrate urine. However, the majority of these patients show mild impairment with a range of specific gravity between

1.019 and 1.022. It will be noted that relatively few patients with mild pre-eclampsia showed evidence of marked renal impairment, but several patients with severe pre-eclampsia showed fairly extensive damage.

TABLE III. CONCENTRATION TEST (133 CASES)

	SPECIFIC GRAVITY			
	1.010-1.016	1.017-1.018	1.019-1.022	1.023-1.030
Mild pre-eclampsia	4	4	23	37
Severe pre-eclampsia	8	5	10	15
Eclampsia	—	—	—	—
Benign essential hypertension	3	3	3	11
Malignant essential hypertension	—	1	3	1
Chronic glomerular nephritis	—	—	1	—
Chronic pyelonephritis	1	—	—	—
Chronic vascular nephritis	—	—	—	—
Total	16	13	40	64

The kidney with very marked impairment cannot bring the specific gravity to a level much higher than 1.010, that of protein-free plasma. Where the concentrating ability of the kidney is below 1.023, it may mean nothing in pregnancy, particularly if the patient is under treatment for toxemia. This is also particularly true in edematous patients with toxemia of pregnancy. Our management of such patients usually involves the limitation of electrolytes, particularly sodium in any form, and the forcing of fluids. In addition, these patients may have been on a low-protein intake before or even have been treated with diets of low-protein content. The concentration test of such patients, therefore, would be of no value in determining the concentrating ability of the kidneys because of the reduction of solute in the urine. This is a consideration not generally recognized or heeded in analyzing the concentration test. In order to obviate such false results in determining the concentrating ability of the kidney, we precede the concentration test with an intake of 5 to 10 Gm. of sodium chloride for one or two days prior to the concentration test, and always after the toxemia has been well controlled. We feel that, where proper precautions are taken, the concentration test gives us one of the very important means of studying renal function in the toxemias of pregnancy. Without such precautions, the test becomes valueless.

#### Dilution Test

The study of the diluting ability of the kidney, although not frequently used, is of value in distinguishing very abnormal kidneys from normal kidneys. The normal kidney can dilute glomerular filtrate to levels of 1.003 to 1.001 or even to 1.000. This is of considerable value in differentiating between extensive and no renal damage. The kidney with severely damaged tubules, in addition to not being able to concentrate, likewise cannot dilute to less than approximately 1.007. In patients with renal insufficiency, it requires a considerably longer time to eliminate extra water whereas this is not true in patients with normal kidneys.

Nine of our total group of patients (Table IV) revealed evidence of marked renal impairment as determined by the dilution test. The majority



of these had mild pre-eclampsia; these findings appear to indicate, on the basis of this particular determination, that these patients were incorrectly classified on the basis of the usual clinical criteria used for classifying toxemias of pregnancy. That marked tubular damage was responsible for pronounced limitation of diluting and concentrating ability in two patients, to between 1.007 and 1.010, was confirmed by a marked reduction of renal blood flow in these two patients.

TABLE IV. DILUTION TEST (135 CASES)

	SPECIFIC GRAVITY		
	1.000-1.003	1.004-1.006	1.007-1.009
Mild pre-eclampsia	35	28	4
Severe pre-eclampsia	24	12	2
Eclampsia	—	—	—
Benign essential hypertension	8	10	2
Malignant essential hypertension	3	3	—
Chronic glomerular nephritis	—	—	1
Chronic pyelonephritis	1	1	—
Chronic vascular nephritis	1	—	—
Total	72	54	9

### Phenolsulfonphthalein Test

This determination of renal function was performed in one hundred patients with toxemia of pregnancy. Almost 60 per cent of all the patients thus studied showed evidence of decreased tubular function as measured by a PSP excretion of less than 50 per cent in one hour. It is seen in Table V that, among those with decreased function, the majority showed evidence of moderate tubular impairment. Of the group showing impaired renal function as determined by the PSP test, 44 per cent, or 25 patients, showed evidence of severe impairment. The most marked changes occurred in mild and severe pre-eclampsia and in primary renal disease. It is interesting to note that none of these changes of marked decrease in renal function was present in the hypertensive group. Two patients showed very high PSP excretions; one excreted 80 per cent of the dye and the other approximately 100 per cent. These probably could be attributed to primary liver disease, by virtue of the failure of the liver to excrete the dye into the bile. Magnesium sulfate does not form a part of the treatment of toxemia of pregnancy among patients in our clinic. Thus the accuracy of the PSP test among the group presented here is not open to the same question as if magnesium sulfate has been administered.

TABLE V. PHENOLSULFONPHTHALEIN—ONE-HOUR COLLECTION (100 CASES)

	29% OR LESS	30-39%	40-49%	50% OR OVER
Mild pre-eclampsia	4	8	19	23
Severe pre-eclampsia	4	—	9	13
Eclampsia	—	—	—	—
Benign essential hypertension	—	3	3	6
Malignant essential hypertension	—	3	1	1
Chronic glomerular nephritis	1	—	—	—
Chronic pyelonephritis	1	—	—	—
Chronic vascular nephritis	—	1	—	—
Total	10	15	32	43

On the basis of our data we are in full agreement with Stander<sup>6</sup> that it is impossible to differentiate mild pre-eclampsia from severe pre-eclampsia or from other types of toxemia of pregnancy by the utilization of the PSP test. However, our results coincide almost exactly with Chesley's figures, in that 43 per cent of all our patients with toxemia excreted normal amounts of dye. Even though Chesley utilized the two-hour test and we used the one-hour, we feel that, on occasion, the two-hour test in pregnant patients does ensure completeness in accounting for maximum excretion of dye. In order to ensure accuracy in performing the test, 6 mg. of sterile phenol red diluted with 9 c.c. of water is injected intravenously. Urine samples are collected, with an indwelling catheter in place, at fifteen minutes and at one hour. Normally 25 per cent of the dye should be excreted at fifteen minutes, and an additional 25 per cent excreted at the end of one hour. During this period the patient drinks between 400 and 500 c.c. of water to ensure adequate urinary output. In normal individuals, the quantity of dye excreted is independent of the urine volume, but with severe renal impairment the dye output is directly proportional to the urine volume, and can be increased with the liberal use of water.

One can readily see here that, with dilatation of the urinary tract, there is reduced ureteral peristalsis, so that there may conceivably be a lag in the appearance of the dye in the bladder urine. Keeping this in mind, values lower than 25 per cent in the fifteen-minute collection may be caused by these extra renal factors; the same could be said of the one-hour collection. It is for this reason that we have added a collection at the end of two hours.

Falls noted that the more severe the toxemia of pregnancy, the lower the excretion of dye. Cadden and McLane<sup>7</sup> failed to recognize any value in the PSP test as a means of differentiating mild and incipient renal disease from the specific toxemias of pregnancy. When compared with other tests of renal function, our evaluation of the PSP test supports the findings of most investigators in that we cannot consider it a sensitive test of renal function.

### Urea Clearance

The urea clearance is the amount of blood (or plasma) in cubic centimeters "cleared" of urea by the kidneys in one minute. To state this another way, the urea clearance is the least volume of blood (or plasma) the content of which is equal to the amount of urea excreted by the kidneys in one minute. Blood urea is present in solution in the plasma. As the blood is filtered through the glomerulus, all the urea goes through as a part of the filtrate. Since urea is of comparatively small molecular weight, some of it easily diffuses through the tubular wall and goes back into the blood stream with the reabsorption of water. The amount of back diffusion actually depends on the rate of urine flow through the tubules. At extremely high urine volumes, very little of the urea is reabsorbed and the filtration rate of urea nearly approaches that of the glomerular filtration rate of inulin. At very low urine

volumes, much of the urea is reabsorbed because of the slow tubular stream; the urea clearance under these circumstances differs very greatly from the glomerular filtration rate of inulin.

The test is performed in the morning and breakfast is withheld. The BUN is constant, and should not fluctuate, as it might if the patient had eaten recently, particularly if the food were of high-protein content. An indwelling catheter is placed in the bladder. The test is begun after the bladder is emptied. Two consecutive hourly samples are taken. During this period of time the patient consumes between 500 and 1,000 c.c. of water, to ensure adequate urinary output. At the collection of each hourly specimen, suprapubic pressure is applied in an attempt to empty the bladder completely. While many state that voided specimens may be used, we routinely employ the catheter because of the high degree of residual urine noted in many of our pregnant patients. The test is performed with the patient at complete bed rest.

Dieckmann found the urea clearance to be significantly low in the antepartum phase among patients with specific toxemia of pregnancy but that the values returned to normal levels during the postpartum period. Chesley<sup>8</sup> and Hurwitz and Ohler<sup>9</sup> state that the urea clearance is normal in pre-eclampsia. Chesley further states that it is normal in eclampsia.

Some authors accept the urea clearance test as valid only when the two specimens agree within 15 per cent of each other, although most allow a margin of 30 per cent agreement between the two specimens. Most of our results (74 per cent) agreed within 15 per cent of each other. The majority of those showing a difference of between 15 and 30 per cent in the two specimens occurred where the urea clearance was greater than 70 per cent of normal.

While the urea clearance determination is widely used and represents a rough index of the glomerular filtration, it may well give false impressions as to the status of the kidney. This is particularly true where tubular damage is present without glomerular damage. Tests of function which reflect only the glomerular filtration rate could yield normal values until renal damage and ischemia are well advanced. Thus the concentration test could theoretically show decreased function (tubular damage) while the "apparent" glomerular filtration rate by the urea clearance is normal. Since both these tests are easily performed and may be consecutively performed, they should constitute the minimum evaluation of renal function in patients diagnosed as having any type of pregnancy toxemia. These two tests are of particular value in evaluating prognosis.

It will be seen in Table VI that observations in our patients with chronic glomerulotubular nephritis, chronic pyelonephritis, and chronic vascular nephritis show full agreement with Chesley's observations. He found that, where the urea clearance test falls below 70 per cent of normal, one can differentiate Bright's disease from pre-eclampsia. In our group of cases, however, it is impossible to differentiate pre-eclampsia in every case, using these tests, from primary renal disease or from the renal impairment incident to the various types of hypertension.

TABLE VI. UREA CLEARANCE, PERCENTAGE OF NORMAL (121 CASES)

	49% AND UNDER	50-69%	70% OR OVER	OVER 70%*	UNDER 70%*
Mild pre-eclampsia	11	9	24	14	6
Severe pre-eclampsia	7	7	10	7	1
Eclampsia	—	—	—	—	—
Benign essential hypertension	3	2	7	2	1
Malignant essential hypertension	2	1	1	1	—
Chronic glomerular nephritis	1	1	—	—	—
Chronic pyelonephritis	2	—	—	—	—
Chronic vascular nephritis	1	—	—	—	—
Total	27	20	42	24	8

\*Difference of 15 to 30 per cent in two specimens.

### Glomerular Filtration Rate

The mean average of the glomerular filtration rate in our patients with pregnancy toxemia<sup>10</sup> is 110 c.c. per minute, corrected to 1.73 square meters of body surface; this is considerably lower than the average value in normal pregnancy. As shown in Table VII, rates of the glomerular filtration do not indicate a true measure of the type of toxemia. They do show evidence of the degree of renal damage, but give no clue to the permanence of such damage. It will be noted that individuals with hypertension and with primary nephritis show consistently reduced levels of glomerular filtration. These reductions are particularly pronounced and probably represent a reflection of severe and sustained damage of long standing. It is in this hypertensive group that we feel the changes are probably primarily arteriosclerotic.

In mild and severe pre-eclampsia, approximately one-third of the patients present evidence of a marked decrease in the glomerular filtration rates. This might be interpreted as being due to afferent arteriolar spasm and, as pointed out in an earlier publication, a return to normal would probably indicate the presence of vasospastic mechanisms.

TABLE VII. GLOMERULAR FILTRATION RATES (CUBIC CENTIMETERS PER MINUTE PER 1.73 SQUARE METERS) (50 CASES)

	0-49 C.C.	50-69 C.C.	70-89 C.C.	90- 109 C.C.	110- 129 C.C.	130- 169 C.C.	170- 199 C.C.	200- 230 C.C.	OVER 1 C.C.
Mild pre-eclampsia	1	3	1	1	2	3	1	1	1
Severe pre-eclampsia	3	1	3	6	—	3	4	4	—
Eclampsia	—	—	—	—	—	—	—	—	—
Benign essential hypertension	2	1	—	—	—	1	—	—	—
Malignant essential hypertension	1	1	1	1	—	—	—	—	—
Chronic glomerular nephritis	1	—	1	—	—	—	—	—	—
Chronic pyelonephritis	2	—	—	—	—	—	—	—	—
Chronic vascular nephritis	—	—	—	—	—	—	—	—	—
Total	10	6	6	8	2	7	5	5	1

### Renal Plasma Flow

Among the patients in whom renal plasma flow was determined, the values were found to be lowered in mild pre-eclampsia. While such levels are not anticipated in this group of patients, they might well represent a danger fore-



cast by the diagnosis of mild pre-eclampsia. The prognosis of these patients appears to be underestimated by the clinical diagnosis of mild pre-eclampsia which implies complete return to normal. It seems entirely likely that this group of mild pre-eclamptic patients, in whom lowered renal plasma flow is found, could develop sequelae compatible with latent hypertensive processes. Even among those who presented normal renal plasma flow levels, these levels were in the *low* normal group. Consequently, only three of our patients with mild pre-eclampsia studied showed evidence of normal or significantly elevated renal plasma flow.

TABLE VIII. RENAL PLASMA FLOW (CUBIC CENTIMETERS PER MINUTE PER 1.73 SQUARE METERS) (49 CASES)

	0-225 C.C.	226- 349 C.C.	350- 474 C.C.	475- 624 C.C.	625- 674 C.C.	675- 724 C.C.	725- 799 C.C.	800- 1100 C.C.
Mild pre-eclampsia	1	4	3	2	1	1	—	1
Severe pre-eclampsia	—	3	4	9	4	1	1	2
Eclampsia	—	—	—	—	—	—	—	—
Benign essential hypertension	—	1	2	1	—	—	—	—
Malignant essential hypertension	2	—	—	—	1	—	—	1
Chronic glomerular nephritis	2	—	—	—	—	—	—	—
Chronic pyelonephritis	2	—	—	—	—	—	—	—
Chronic vascular nephritis	—	—	—	—	—	—	—	—
Total	7	8	9	12	6	2	1	4

On the other hand, in severe pre-eclampsia the renal blood flow was characteristically normal or well above normal. This would lead us to suggest that perhaps the mechanisms involved in severe pre-eclampsia are such as to indicate a lesser or even absent degree of renal arteriolar spasm in the efferent glomerular arteriole.

Among the patients with diseases not related to pregnancy, not only was renal plasma flow markedly diminished as anticipated in the various types of essential hypertension, but tremendously low levels were encountered in chronic glomerulotubular nephritis and chronic pyelonephritis. This seems to indicate that the primary factor in these nephritides is efferent arteriolar vasoconstriction or advanced tubular damage. However, the advanced tubular damage could well be on the basis of primary vascular damage anywhere in the kidney, whether afferent or efferent. This is borne out by the very marked impairment of glomerular filtration in this latter group, in whom the rates were among the lowest obtained in the entire series.

### Conclusions

1. An analysis of the various renal function studies used in toxemia of pregnancy is presented.
2. The blood urea nitrogen is not ordinarily elevated in toxemia of pregnancy; on the other hand, it is usually somewhat lower than the generally accepted normal for pregnancy which appears to indicate possible hepatic pathology.

3. The urea clearance test is a satisfactory method as a rough index of determining glomerular filtration ability.

4. The concentration test is the most satisfactory means of determining tubular integrity.

5. The combination of the concentration test and the urea clearance test will give satisfactory information regarding prognosis.

6. The clinical classification of toxemia of pregnancy does not offer an accurate index of the underlying physiopathologic process.

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## THE BULBAR CONJUNCTIVAL VASCULAR BED IN THE TOXEMIAS OF PREGNANCY\*†

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FOR THE past forty years evidence has accumulated indicating that the peripheral vascular bed undergoes a marked change in toxemia of pregnancy. Irving<sup>1</sup> in 1936 popularized the belief that toxemia is not a disease of any individual organ but is an affection of all the terminal arterioles. Eastman<sup>2</sup> in 1937 summarized much of the pathological and clinical evidence supporting the importance of the vascular factor in the toxemias. McKelvey<sup>3</sup> studied the arterioles in the decidua basalis. He noted the appearance of fibrinoid change in the arteriolar walls and aneurysmal dilatations in the placenta in normal pregnancy and in premature separation of the placenta. Hertig<sup>4</sup> described autopsy studies in toxemia and stated that in his opinion the fundamental disturbance is in the wall of the terminal arteriole. Sheehan and Moore<sup>5</sup> indicated in their recent monograph on renal cortical necrosis that the initial characteristic changes are spasm of the interlobular renal arteries and the afferent arterioles of the glomerulus. Direct observations of the uteroplacental vascular bed during normal or toxemic pregnancy are unknown. Studies of peripheral vessels have been limited to the nail bed<sup>6</sup> and the retina.<sup>7</sup> Both of these areas have demonstrated arteriolar constriction in the toxemias. In addition, recent anatomical studies<sup>8</sup> indicate that the nail bed vessels are not true capillaries but rather arteriovenous shunts. Also, the nail beds have been exceedingly difficult to photograph. The variations in the retinal arterioles have proved helpful as an aid in diagnosis and clinical evaluation, particularly in the more advanced toxemias. However, in the retina with the ordinary ophthalmoscope, the terminal arterioles, venules, and capillary vessels are not viewed. Because of the accessibility and ease of photography, we selected to study the terminal vascular bed, arterioles, venules, and capillaries of the bulbar conjunctiva in normal and toxemic pregnancy.

The peripheral circulation of the bulbar conjunctiva exhibits progressive changes during the course of normal pregnancy and the puerperium.<sup>9</sup> Arterioles show a gradual constriction with a reduction in blood flow that is most prominent in the third trimester. During labor certain of the fine arterioles develop a Grade I spasm. Blood flow in the venules in the second trimester appears "granular" over the entire vascular bed; this reaches a maximum in the last month, during labor, and for the initial three days post partum. The

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blood flow in the capillary bed progressively diminishes and the number of vessels visualized is significantly reduced during the later months of pregnancy until approximately the fifth day of the puerperium. This group of initial findings in the normal primipara and multipara will be compared with the various vessel changes visualized in the different types of toxemia. In addition, certain distinct abnormalities of the finer vessels seen in vascular disease associated with the toxemias will be described.

### Methods and Terminology

The bulbar conjunctival vessels are observed with a slit lamp and binocular microscope, with the observer in the sitting position. The most convenient magnification for routine use is 50 $\times$ , although higher magnification may be used up to 144 $\times$ . A 35 mm. reflex camera is attached to the barrel of the microscope, including the ocular and F2.0 lens. Black-and-white or color film may be used. The vascular pattern selected for photography is brought into accurate focus with the slit lamp as the light source. The focal plane shutter is synchronized at a speed of  $\frac{1}{50}$  second with a strobe light of 180 watt seconds.

Certain terms frequently used to simplify description in the text will be explained further. Vasomotion is a wavelike undulating motion seen along the course of the arterioles. In a more advanced form, this vasomotion blends into mild spasm or Grade I vasoconstriction or vasospasm. True "bulb" formation with intervening arteriolar constriction is classified as Grade II spasm. Grade III spasm is associated with marked areas of arteriolar thinning and large bulbous swelling which is frequently asymmetrical. A generalized reduction of the arteriolar caliber, with thinning of the lumen throughout its entire course, is known as attenuation. At times the blood flow in the peripheral vascular bed is reduced and many capillaries are emptied of blood. This condition is known as ischemia and is likewise graded as to degree. Slowing of blood flow in the capillaries and venules is manifested by granular flow. When this alteration in the character of flow becomes extreme, large clumps of red cells appear in aggregates separated by clear areas which contain plasma. In advanced essential hypertension, the capillaries are elongated and have the appearance of a coil. This is described as tortuosity of the capillaries.

### Results

Our previous study of the bulbar conjunctival vessels in 100 normal primiparas and multiparas clearly demonstrated arteriolar spasm of a mild nature in the second and third trimesters. About 50 per cent of the patients had no such spasm while the remaining patients showed a Grade O-I. A few patients demonstrated a transient Grade II spasm close to term or during labor. These phenomena disappeared almost completely during the first week post partum.

TABLE I. CONJUNCTIVAL STUDIES IN PREGNANCY

Normal	100	
Toxemia	155	
Mild pre-eclampsia		53
Severe pre-eclampsia		20
Mild hypertension		29
Severe hypertension		20
Eclampsia		8
Diabetes		16
Renal disease		9
Total	255	



In Table I are listed the number under each variety of toxemia and the normal group<sup>9</sup> which were studied with the slit lamp microscope over the course of pregnancy. The criteria for classification were based on the definitions suggested by the American Committee on Maternal Welfare, April 1, 1952.

1. *Vasospasm*.—In the milder instances of pre-eclampsia (Fig. 1), approximately one-fourth of the patients had no evidence of spasm, 20 per cent showed a more severe degree, Grade II, and the remainder demonstrated a mild Grade I type of spasm. In severe pre-eclampsia, all patients showed some evidence of this phenomenon. Forty per cent of this group with advanced toxemia manifested a Grade II spasm and 60 per cent a mild degree of this change. In essential hypertension, the degree of spasm was closely correlated

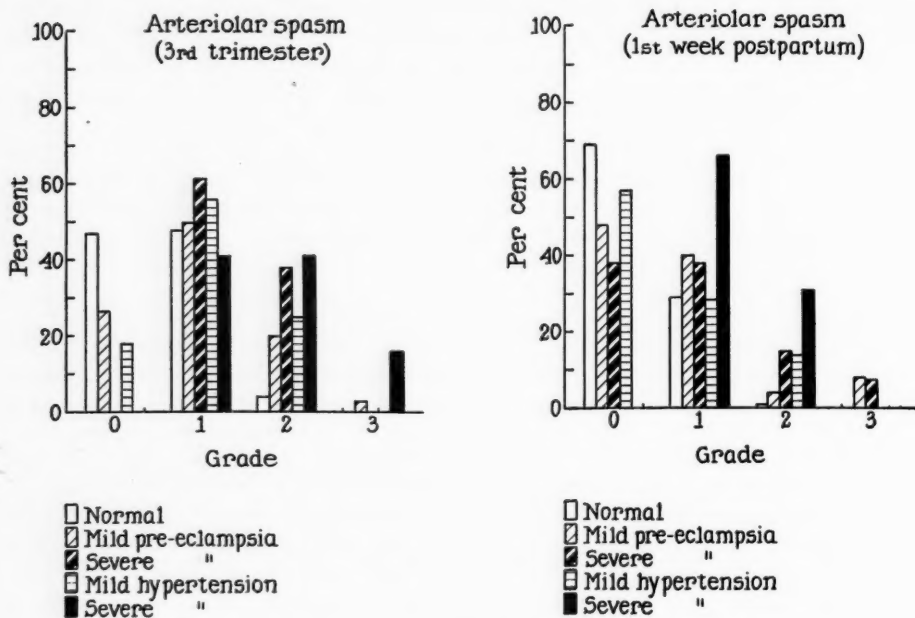


Fig. 1.

Fig. 2.

with the blood pressure elevation. In mild hypertension (diastolic of less than 110), 20 per cent exhibited no spasm, 55 per cent a Grade I, and 25 per cent a Grade II. In severe hypertension, however, all patients displayed arteriolar spasm; 42 per cent showed a Grade I, 42 per cent a Grade II, and 16 per cent a very severe Grade III. With all varieties of toxemia, the spasm decreased rapidly following delivery (Fig. 2). The "vascular relaxation" was in direct relationship to the severity of the toxemia during pregnancy. As can be seen on the accompanying graphs, the severely hypertensive patients continued to demonstrate considerable spasm which persisted indefinitely. Two cases are briefly presented demonstrating spasm which increased in severity close to term.

J. S., No. 573 407. Essential hypertension. This 27-year-old primipara was delivered in the thirty-sixth week of a 2,200 gram normal female infant by low-flap section because of a persistently high blood pressure. During the first trimester, the blood pressure aver-

aged 190/115, in the second 170/110, and in the third 180/120. The retinal vessels showed Grade II changes with marked generalized spasm. The conjunctival vessels also demonstrated severe arteriolar spasm, Grade II-III. The other prominent features were a Grade III granularity in the venules and a Grade III capillary tortuosity. Fig. 3 indicates the extensive arteriolar spasm, capillary tortuosity, and venular granularity.

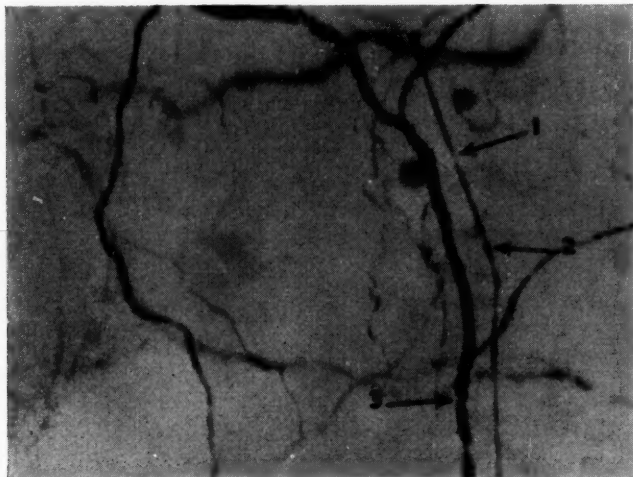


Fig. 3.—J. S. Essential hypertension, third trimester. 1, Grade II arteriolar spasm. 2, Spasm with bulb formation. 3, Venular granularity.

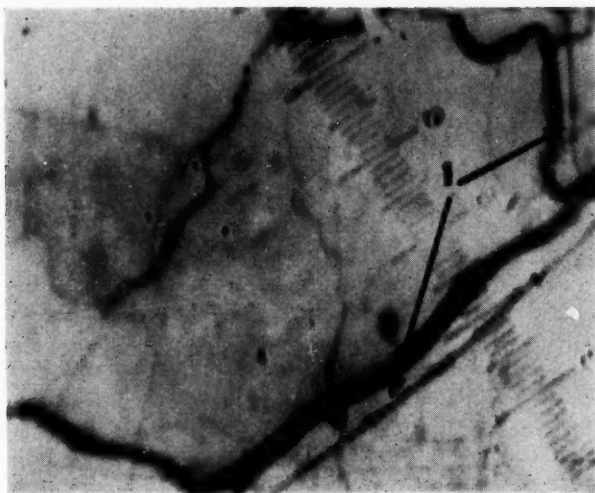


Fig. 4.—F. B. Essential hypertension, second trimester. 1, Grade II arteriolar spasm.

F. B., No. 585 061. Essential hypertension. This 24-year-old para ii, gravida iii, delivered a normal infant of 2,500 grams in 1949. The pregnancy was complicated by pre-eclampsia. The present pregnancy (1952) was associated with a blood pressure of 180/120 in the first trimester, 160/110 in the second, and 180/120 in the third. A 1 plus albuminuria developed at the thirty-sixth week. A 1,670 gram normal male infant was born spontaneously in the thirty-eighth week. The retinal vessels showed advanced Grade II changes with generalized spasm. The conjunctival vessels demonstrated a Grade II localized spasm of the arterioles and a generalized capillary tortuosity, Grade III (Fig. 4).

2. *Tissue Ischemia.*—Beginning in the second trimester of normal pregnancy there was a progressive reduction of the patent and functioning conjunctival capillaries. By the third trimester 85 per cent of the normal patients exhibited moderate capillary ischemia. This was maintained through the first postpartal week without change and then gradually diminished during the subsequent two months to resume the usual vascular state of "normality." Mild and severe pre-eclampsia follow the normal pattern, showing a slight general increase. The hypertensive group evidenced more profound ischemia during the antepartum period. Post partum, in severe hypertension,

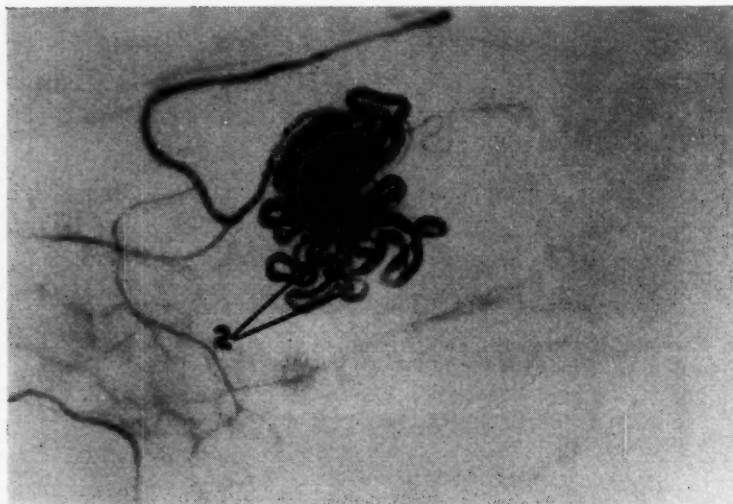


Fig. 5.—L. C. Mild pre-eclampsia, extensive ischemia. 2, Aneurysmal pockets in a coiled venule.

a marked increase occurs in ischemia (75 per cent demonstrating a maximum Grade III). The severely hypertensive group maintains this capillary ischemia indefinitely post partum, whereas in pre-eclampsia and normal pregnancy, a return to the normal peripheral capillary bed is completed within a six-week period. One case of pre-eclampsia is presented demonstrating this extensive ischemia, Grade III.

L. C., No. 627 175. Mild pre-eclampsia. This 18-year-old primigravida developed hypertension with a blood pressure of 140/90, excessive weight gain, and albuminuria in the thirty-second week of pregnancy (Aug. 13, 1952). Four weeks later labor was induced and a normal female infant that weighed 3,050 grams was delivered. The retinal vessels showed a Grade I spasm. The conjunctival vessels disclosed a Grade I spasm in the arterioles. Small bead aneurysms were visualized in a tortuous venule. This venule is surrounded by an area of ischemia, Grade III. Fig. 5 demonstrates the marked ischemia and the stagnant venous blood, related in part to slowing of blood flow.

3. *Alterations in the Character of Blood Flow.*—Granularity was prevalent during normal pregnancy in the conjunctival vascular bed, beginning in the second trimester and progressively increasing during the third, and was maintained throughout the first week post partum. Ninety-five per cent of the

normal group showed this granular appearance of the blood stream in the later stages of pregnancy, with 56 per cent exhibiting Grade III severity. There was very little difference between the normal group as compared to those with toxemia. However, some definite increment in this granularity, particularly among the more severely hypertensive patients (77 per cent exhibiting Grade III), was apparent. In renal disease, however, with reduced renal function and elevated blood nitrogen, there occurred widespread granularity unassociated with spasm or ischemia. This has usually been evident early in the first trimester of the pregnancy. One representative photograph (Fig. 6) demonstrates this granularity and a short case history is detailed.

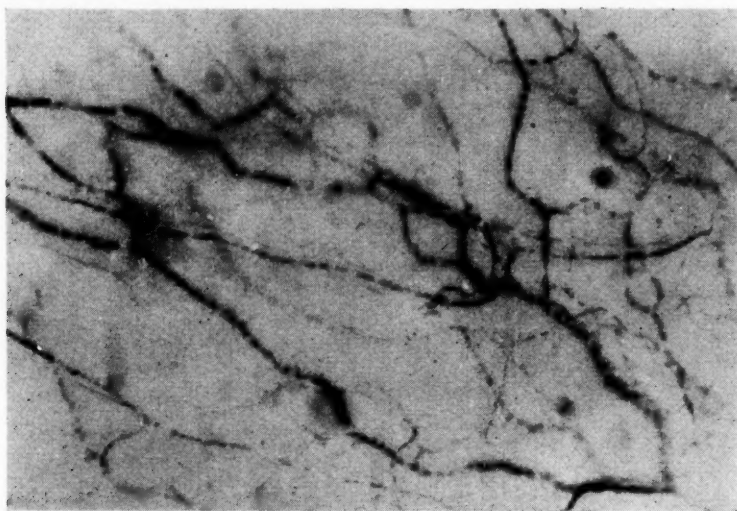


Fig. 6.—G. K. Chronic nephritis, first trimester. Generalized Grade III granularity.

G. K., No. 645 952. Chronic nephritis. This 27-year-old para ii, gravida iii, delivered an 1,850 gram normal female infant in the fortieth week of pregnancy (Jan. 3, 1953). At this time the blood pressure was 110/80 and the urine contained a 2 plus proteinuria. The nonprotein nitrogen was 57 and the phenolsulfonphthalein test showed only a 35 per cent dye excretion. The maximum concentration of urine was 1.012. The retinal vessels showed a Grade I change. The conjunctival vessels demonstrated a generalized granularity. No arteriolar spasm was seen and the arteriolar blood flow was segmented. All capillary blood flow appeared very granular.

4. *Capillary "Tortuosity."*—Tortuosity, when present, remained unchanged during normal pregnancy. In the normal group a Grade O-I has proved common. The group with mild pre-eclampsia followed the same general pattern but 40 per cent of the patients with both mild and severe hypertension showed more than a Grade I. Among the severely hypertensive patients, one-third have the maximal tortuosity (Grade III). Those with severe pre-eclampsia ranged between the normal and hypertensive groups (Fig. 7). Tortuosity, although it remained unchanged, varied visibly as capillary ischemia increased in later pregnancy. One example of extensive tortuosity, associated with eclampsia, is demonstrated.



H. K., No. 595 415. Eclampsia. A 24-year-old primipara, with a normal antepartum course and no history of hypertension, suddenly developed convulsions in the twenty-seventh week of pregnancy (March 19, 1951). The maximum blood pressure was 175/110; albumin in the urine averaged 6 Gm. per liter; retinal arterioles exhibited Grade II changes. In the thirty-second week a 1,000 gram macerated female infant was delivered. The conjunctival vessels showed a Grade II arteriolar spasm with marked attenuation and segmentation of flow. The veins exhibited Grade II granularity. The capillaries in the left eye manifested Grade III tortuosity. Fig. 8 shows this extreme capillary tortuosity.

Certain unusual features have been observed in the conjunctival vascular bed. In several instances true petechial hemorrhages, unassociated with trauma, have been visualized. One hemorrhagic area was seen in a case of eclampsia, three in severe hypertension with advanced vascular disease, and one in pre-eclampsia. In two cases of severe hypertension, aneurysmal dilations of deep scleral veins have been observed. In four instances thrombi have been seen in acute toxemias. These thrombi fade during the first week post partum. Representative cases follow illustrating these three abnormalities.

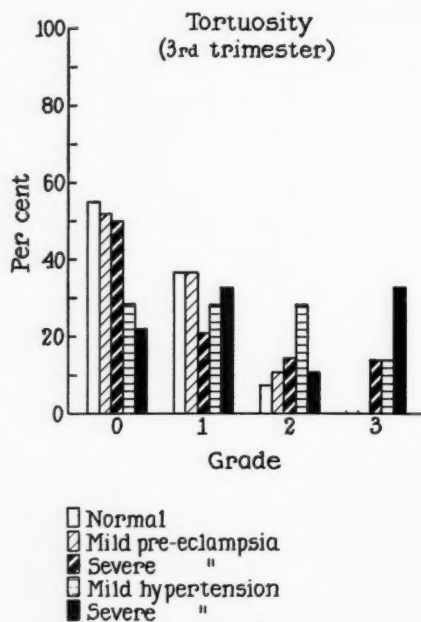


Fig. 7.

F. T., No. 614 326. Essential hypertension. A 41-year-old para iv, gravida iv, delivered a normal male infant on May 14, 1952. Blood pressure levels averaged 155/90 with a high of 180/100 in the thirty-fifth week. The retinal arterioles showed a Grade I plus change. The conjunctival vessels exhibited Grade I plus arteriolar spasm, Grade III ischemia and Grade III granularity. There were multiple aneurysms in the scleral veins (Fig. 9).

A. C., No. 620 208. Mild pre-eclampsia. A 22-year-old para ii, gravida ii, developed hypertension (160/100) in the thirty-sixth week of pregnancy (July 14, 1952). A normal infant that weighed 2,720 grams was delivered in the thirty-seventh week. The retinal vessels showed Grade I changes. The conjunctival vessels likewise demonstrated a Grade I plus spasm and minimal ischemia. Four petechial hemorrhages were seen in the left eye (Fig. 10). These disappeared following the first week post partum.

I. C., No. 627 264. Mild pre-eclampsia. A 30-year-old primigravida developed an elevated blood pressure of 155/100 in the thirty-fifth week of pregnancy, a 4 plus edema and a 2 plus albuminuria (April 30, 1952). Five weeks later spontaneous labor resulted in the delivery of a 2,530 gram normal male infant. In this case, the conjunctival vessels showed a marked ischemia of Grade III, almost obscuring a Grade O-I spasm of the arterioles and the blood flow in the venules was granular Grade III. In one small venule an area of stationary red cells apparently developed into a thrombus (Fig. 11), which grew larger from the thirty-fifth to the thirty-ninth week and diminished during the first week post partum.

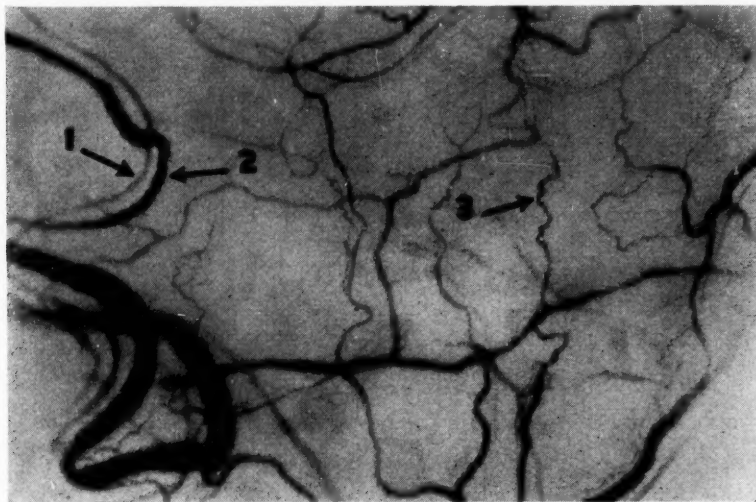


Fig. 8.—H. K. Eclampsia, post partum. Grade III tortuosity. 1, Arteriole. 2, Venule. 3, Capillary.



Fig. 9.—F. T. Essential hypertension. 2, Aneurysmal dilatation of a deep venule.

In the eight patients with eclampsia, conjunctival changes of an abnormal pattern were visualized in all but one. The latter had a postpartum convulsion and could not be observed until several days after the episode. The average

spasm observed was Grade II with excessive ischemia Grade III. This ischemia, in several instances, became so marked that no capillaries and only an occasional arteriole could be seen in the bulbar conjunctival vascular bed. The retinal arteriolar findings, in general, corresponded to the spasm observed in

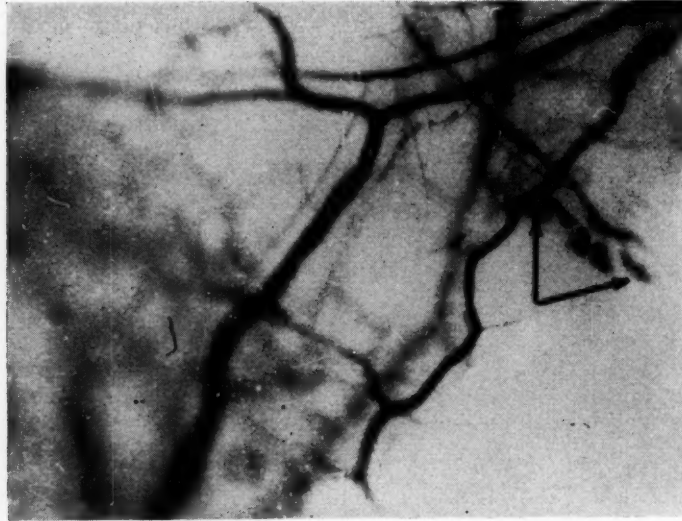


Fig. 10.—A. C. Mild pre-eclampsia, petechial hemorrhages.

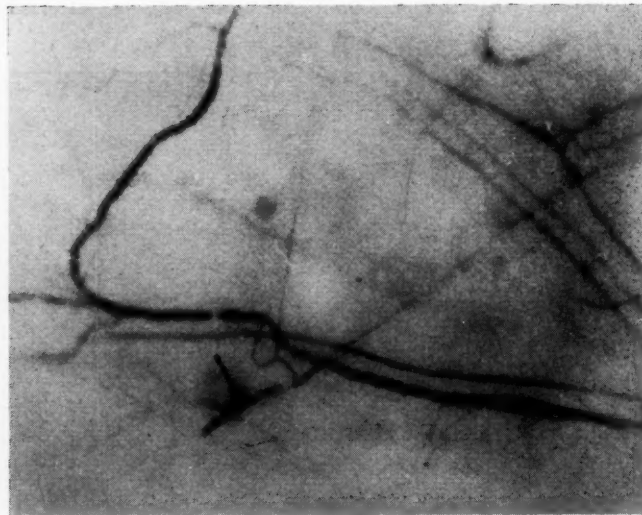


Fig. 11.—I. C. Mild pre-eclampsia. Intravascular thrombus in a small venule.

the conjunctival vessels. The ischemia and spasm are maintained for at least a week post partum in the conjunctiva. The retinal vessels return toward the normal state at a more rapid rate, apparently related to the relative size of the vessels in the two areas.

B. C., No. 628 575. Eclampsia. This 39-year-old primigravida developed hypertension with a blood pressure of 190/110, 4 plus albuminuria, 3 plus edema, and a convulsion in the twenty-fifth week of pregnancy. Twelve days following admission the fetal heart beat was not heard and two days later a 1,080 gram deadborn infant was delivered spontaneously. Retinal vessels showed a Grade I change with some peripheral attenuation. The conjunctival vessels exhibited a Grade II spasm of the arterioles. Ischemia was maximum and only an occasional arteriole and venule were seen prior to delivery. No capillary tortuosity was visualized. Fig. 12 depicts the profound and abnormal ischemia which was the outstanding feature of the conjunctival circulation. The arrow indicates the arteriole which is barely visible due to the marked vasoconstriction. Urinary findings and blood pressure returned to normal values two weeks following delivery.

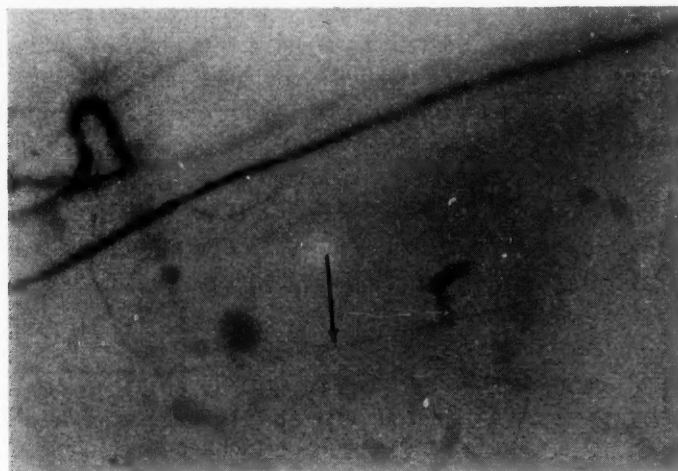


Fig. 12.—B. C. Eclampsia, twenty-sixth week (five days prior to delivery). Extensive ischemia

In the sixteen diabetic patients studied, various degrees of toxemia existed. The spasm seen in the arterioles of the conjunctiva and in the retinal vessels was quite comparable. However, the retinal areas showed evident diabetic retinopathy in three cases. In the conjunctiva, vascular alterations associated with diabetes have been seen as capillary aneurysms by McCulloch and Pashby<sup>10</sup> and Friedenwald.<sup>11</sup> No conjunctival aneurysms were observed in our group.

In advanced renal disease with hypertension, albuminuria, and increased blood nitrogenous elements, the vessels in both the retina and conjunctiva showed comparable spasm. In early pregnancy renal insufficiency without hypertension resulted in an extensive granularity of the conjunctival vascular bed; this was not associated with spasm or ischemia and was usually accompanied by a reduction of albumin and inversion of the albumin-globulin ratio.

In severe hypertension, retinal and conjunctival arterioles both showed, with few exceptions, advanced degrees of spasm. In the second trimester, the spasm in the conjunctiva appears more severe than seen in the retinal vessels. In the earlier months of pregnancy, this was related most likely to greater filling in the conjunctival circulation. Close to term the ischemia and attenuation of the arterioles became so extensive that it interfered with the visualization



of spasm in the conjunctival arterioles. In pre-eclampsia, the same relationship existed between the two vascular zones observed. The conjunctiva again will show more advanced spasm earlier in the pregnancy.

### Comment

From an analysis of these changes in the peripheral vascular bed in the normal and toxemic groups, it is apparent that similar vascular phenomena occur in both conditions with a further advancement in the abnormal pregnancies. In the more extensive toxemias, ischemia is so generalized that spasm becomes difficult to visualize. This is due to the fact that the entire caliber of the vessels is extremely narrowed and attenuated, and the outline of the vessel wall is difficult to delineate. In several instances of eclampsia and severe pre-eclampsia, no arterioles could be distinguished and the vascular bed became almost bloodless with only a few scattered small venules containing slow-moving or stagnant red blood cells. It thus becomes evident that the process of reduced blood flow and vessel attenuation diminishes the chances of visualizing the process of spasm as it extends to the maximum limits.

The presence and extent of granularity do not vary diagnostically in the normal, pre-eclamptic, or hypertensive patients and it becomes more progressive as pregnancy proceeds toward term. If maximum granularity is seen early in pregnancy, it may accompany renal insufficiency. This has been seen consistently in all nine patients. If the pregnancy is interrupted, the process of progressive granularity associated with the renal insufficiency becomes less evident.

Tortuosity of the capillaries, if extensive, is strongly indicative of vascular disease and essential hypertension.<sup>12</sup> It may well be that some of the patients with milder pre-eclampsia and hypertension who show Grade II tortuosity will in later years develop high blood pressure and a more advanced form of essential hypertension.

Small areas of conjunctival hemorrhage have been seen only in eclampsia, hypertension, and pre-eclampsia. This phenomenon has not been observed in the normal group. It certainly suggests a serious form of the toxemic vascular process. It may well indicate a physiological process similar to retinal hemorrhage.<sup>13</sup> The presence of venous aneurysmal dilatation has been seen only in patients with essential hypertension and this may indicate evidence of vascular damage associated with the disease. Only rarely have small thrombi been visualized and these probably represent small areas of intravascular clotting. This may be caused by some aberration of the clotting mechanism with the possible release of thromboplastin.<sup>14</sup> However, one recent case of hypertensive toxemia exhibiting intravascular clotting showed normal blood fibrinogen levels.

The recent observations of Bartholomew<sup>15</sup> and Bonsnes,<sup>16</sup> in our own institution, show that albuminuria is present during labor in from 53 to 62 per cent of normal pregnancies. This is suggestive evidence that widespread vascular changes are taking place in the body. The maximum effect of such

processes are brought to light by the work of Sheehan.<sup>17</sup> The afferent arteriolar spasm in the kidney may vary considerably in intensity. With spasm at its maximum, a complete shutdown of arteriolar blood supply may occur with ischemic necrosis of both kidneys. This identical process with minimal effect also may be indicated by the frequent albuminuria of labor. Mack and his co-workers<sup>18</sup> have demonstrated the changes in plasma proteins during normal pregnancy. In toxemic pregnancy, there is an additional change in the various plasma protein fractions, probably representing further modifications which are physiologic in pregnancy. These authors show the additional increase in fibrinogen,  $\alpha_2$ , and globulin and the decrease in gamma globulin and albumin which are usually associated with toxemia. As in the alterations in the conjunctival vascular bed, the plasma proteins return to normal nonpregnant levels after the sixth week post partum.

The conjunctival vascular bed in toxemia demonstrated a further reduction in blood flow as compared to the normal group, becoming maximal in eclampsia. In this condition the spasm is frequently so severe that peripheral arteriolar flow is absent and capillaries are not visualized, resulting from the absence of any red blood cells in the capillary bed itself. McCall<sup>19</sup> has shown an increase in vascular resistance of the cerebral arterioles in eclampsia, probably related to a similar constriction of the cerebral arterial circulation. The complete blockade of renal arteriolar circulation may account for renal cortical necrosis. We have no direct evidence of the exact anatomical change which occurs in the peripheral circulation of the kidney, brain, and liver. The possibility exists that similar phenomena, which we have viewed directly in the conjunctiva and described in this communication, occur elsewhere in the body.

McKay and his co-workers<sup>20</sup> have recently supported the idea that the basic pathological process in the advanced toxemias is a generalized fibrin embolism. In the autopsy material at the Boston Lying-in Hospital, sections indicate such intravascular thrombi throughout the body, principally in the liver, kidney, lung, and brain, surrounded by local tissue necrosis and hemorrhage. These authors believe that the embolism is associated with the release of a thromboplastic substance from the placental site which produces intravascular clotting. In our study of the conjunctival vascular bed in toxemia, four instances of intravascular thrombus formation were observed. It is our opinion that the extensive processes of arteriolar spasm and capillary ischemia are the important findings rather than intravascular thrombosis. Furthermore, in the toxemias, particularly in the acute and severe varieties, there is an increase in fibrinogen rather than a decrease.<sup>18</sup> From our experience with the terminal conjunctival vascular bed, it appears that the peripheral vascular disturbance in the toxemias is principally a spasm of the arterioles resulting in a slowing and diminution of the terminal circulation. This reduction in blood flow and the increased fibrinogen may give rise secondarily to some intravascular clotting and thrombus formation.

Epinephrine has been applied to the conjunctiva topically in various dilutions to determine the minimal concentration producing constriction. In

general, the sensitivity to this drug increases as the spasm and ischemia become more evident, particularly during the last eight weeks of pregnancy. The epinephrine sensitivity, likewise, is slightly higher in the toxemias than in normal pregnancy. In three patients who received Apresoline,\* the conjunctival circulation was observed. In one patient 60 mg. of Apresoline was injected intravenously, the blood pressure dropped from 170/110 to 140/90, and the patient complained of nausea and a generalized headache. The conjunctival vascular bed was observed before and after the Apresoline injection and no changes in spasm or ischemia were noted and blood flow was unaltered. It is suggested that the hypotensive effect of Apresoline may not be in the terminal vascular bed, but may be associated with a dilatation of larger vessels.

The conjunctival vascular changes seen in the toxemias may be considered as another clinical criterion in evaluating the progress and severity of the abnormal process. From all the data presented, it is obvious that the phenomena found gradually progress from normal findings to various degrees of abnormality. None of the clinical observations used to measure the severity of the toxemia has any real specificity. Transitory blood pressure elevation, albuminuria, and edema may be found in many so-called normal patients. Minimal conjunctival derangements are similarly apparent in many normal pregnancies, and may be more advanced close to term. A Grade II spasm seen in the second trimester would be of clinical significance, whereas, if found in labor, the interpretation would depend on the other clinical findings. The presence of complete blanching of the capillary bed, Grade III spasm, petechial hemorrhages, and thrombus formation is definite evidence of abnormal processes. The presence of high-grade capillary tortuosity and venular aneurysms also suggests inherent vascular disease and perhaps introduces additional evidence for an unfavorable prognosis for the fetus. These facts add information potentially useful in evaluating the case and permitting closer supervision of the clinical course. As our experience grows with the use of this new method for examination of the terminal vascular abnormalities in the toxemias, more definitive clinical criteria may be established. Furthermore, the effect on the peripheral vascular bed in normal and toxemic pregnancy of the large number of new antihypertensive and ganglion-blocking agents may be more completely studied and evaluated.

### Conclusions

1. In the toxemias of pregnancy there is a further progression of the conjunctival vascular changes visualized in normal pregnancy.
2. The changes in the vascular bed in the toxemias appear earlier and more advanced in the conjunctiva as compared to the retina.
3. Spasm and ischemia increase in the severe toxemias and reach a maximum in eclampsia.
4. Except for extensive renal disease, granularity does not vary diagnostically in the normal from the toxemic patient.

\*1-Hydrazinophthalazine hydrochloride—Ciba Pharmaceutical Products, Inc.

5. Tortuosity of the capillary bed remains unchanged in normal and toxemic pregnancy and is most consistently seen in severe hypertension and severe pre-eclampsia.

6. The more extensive vascular alterations persist for about one week following delivery and in some instances appear more severe for the first three days post partum. These changes, except in the hypertensive group, gradually decrease and return to the nonpregnant level within six weeks post partum.

7. When diabetes is associated with toxemia, vascular conjunctival changes are apparent. Capillary aneurysms in the conjunctiva reported in diabetics have not been seen in the present series.

8. Certain findings, such as venular aneurysms, intravascular thrombi, and small hemorrhages, are further evidences of vascular disease and are occasionally seen in the advanced toxemias.

9. When essential hypertension existed prior to pregnancy, spasm and ischemia recede partially during the postpartum period and the changes associated with hypertension persist indefinitely.

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## CAUSES OF DEATH IN FIVE HUNDRED THIRTY-THREE FATAL CASES OF TOXEMIA OF PREGNANCY

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**T**OXEMIA of pregnancy continues to be a major problem to those interested in maternal welfare. In 1937 it accounted for 33 per cent of all maternal deaths in the state of North Carolina.<sup>1</sup> Although this figure has now dropped to 26 per cent, toxemia is still the most frequent cause of death in our state.

Despite the frequency of this complication, little is known about its etiology and pathogenesis. Current literature is replete with articles concerning its treatment, classification, and incidence. A number of theories concerning the etiology have been proposed, but so far none has been wholly acceptable. As a consequence, therapy is largely symptomatic.

A review of the 1,500 maternal deaths which occurred in North Carolina between Aug. 1, 1946, and Jan. 1, 1953, showed that 533 deaths were related to toxemia of pregnancy. Toxemia was considered the direct cause of death in 393 cases and a contributing factor in 140 additional deaths which were primarily due to some other complication, such as hemorrhage.

Although all physicians practicing obstetrics have had experience with toxemia, few have observed a large number of fatal cases. For this reason little information regarding the course of fatal toxemia is available. The data obtained in the North Carolina survey were studied with this fact in mind.

### Method of Investigation

The Committee on Maternal Welfare of the Medical Society of the State of North Carolina has reviewed all maternal deaths reported in the state since August, 1946. The details of the method of investigation have been reported elsewhere.<sup>2, 3</sup> Since the survey has been conducted largely by questionnaire and correspondence, some records are incomplete. Despite this drawback, the data compare favorably with those obtained by other methods.

No case was included in this survey of deaths from toxemia unless a definite record of hypertension was given. On the other hand, deaths from causes unrelated to toxemia were not included even when hypertension was present. Autopsy reports were available in 21 cases.

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### Clinical Findings

The immediate cause of death in each case was determined on the basis of clinical information obtained from the record. Since there was a considerable degree of overlapping, only the complications of greatest significance were listed as primary or contributing causes of death (Table I).

TABLE I. IMMEDIATE CAUSES OF MATERNAL DEATHS IN WHICH TOXEMIA WAS A PRIMARY OR CONTRIBUTORY FACTOR

	PRIMARY	CONTRIBUTORY	TOTAL
Cerebral dysfunction	180		180
Pulmonary edema	115	18	133
Renal failure	20	10	30
Hemorrhage		39	39
Pulmonary embolism		29	29
Infection		18	18
Anesthesia		12	12
Other	5	11	16
Unknown	73	3	76
Total	393	140	533

Marked cerebral disturbances were the predominant symptoms in 180 patients whose deaths were attributed primarily to toxemia. Eighty-nine of these patients exhibited gross evidence of intracranial hemorrhage, such as hemiplegia or bloody spinal fluid. In 73 cases sudden death, preceded by respiratory arrest and cyanosis, occurred during a convulsion. Coma, with or without antecedent convulsions and in the absence of any other explanation, accounted for the remaining 18 deaths in this group.

Pulmonary edema appeared to be the crucial factor in 133 of the deaths related to toxemia. These patients exhibited one or more typical attacks of pulmonary edema and died in a state of deep cyanosis during an attack. In approximately 18 per cent of these cases a precipitous drop in blood pressure and a slow, weak pulse were noted prior to the clinical appearance of pulmonary edema. Some form of antecedent organic heart disease was present in the 18 patients in whom toxemia was considered only a contributory cause of death.

Severe oliguria or anuria, leading to progressive uremia, was responsible for 30 deaths. Pulmonary edema occurred as an agonal event in most of these cases. Death occurred four to ten days after the onset of the renal suppression. Oliguria and anuria were recorded in 44 additional patients, whose deaths occurred so soon after the onset that the renal shutdown was not considered to be a major factor. Premature separation of the placenta preceded renal suppression in the 10 cases listed in the "Contributory" column. In these cases toxemia was present, but on the basis of blood pressure, urinary findings, and clinical symptoms, was considered mild.

Toxemia was a contributory factor in 109 deaths which were attributed primarily to hemorrhagic shock, pulmonary embolism, puerperal sepsis, or anesthesia. Of the 5 remaining deaths, one was due to aspiration of gastric contents during a convulsion, one to gastric hemorrhage, one to hepatic failure,

and two to unexplained shock occurring during a traumatic delivery. In 76 cases clinical information regarding the events immediately preceding death was not sufficient for classification.

### Pathologic Findings

Autopsy reports were available in 21 cases and the findings are shown in Table II. All of the noteworthy postmortem findings are recorded, without regard to the severity of the changes or their importance as a cause of death. In 8 cases the brain was not examined, and in two of these the autopsy was incomplete in other respects.

Data from the series published by Acosta-Sison<sup>4</sup> and Way<sup>5</sup> are included in Table II for purposes of comparison. It was possible to compare the findings

TABLE II. AUTOPSY FINDINGS IN MATERNAL DEATHS DUE TO TOXEMIA

	SERIES OF ACOSTA-SISON	SERIES OF WAY	SERIES NORTH CAROLINA	TOTAL
<i>Heart.</i> —				
Hemorrhage	1	12	4	17
Necrosis	1	4	1	6
Hypertrophy and/or dilatation	9		5	14
Myocarditis	1	2	1	4
Endocarditis	1	1		2
<i>Brain.</i> —				
Hemorrhage	1	3	5	9
Edema	2		3	5
Arteritis		4	1	5
Necrosis		1	2	3
Pituitary necrosis			1	1
<i>Liver.</i> —				
Focal necrosis	28	29	14	71
Petechial hemorrhage	36		6	42
Fatty change	9			9
Hepatitis			2	2
<i>Kidneys.</i> —				
Acute parenchymatous degeneration	13			
Necrosis, hemorrhagic	2			
Acute and subacute nephritis	7			
Chronic nephritis	15			
Cortical necrosis			3	
Abscess			1	
Way classification				
Stage I		11	9	
Stage II		16	4	
Stage III		6	2	
<i>Lungs.</i> —				
Pulmonary edema	14	16	11	41
Pneumonia	2	16	7	25
Hemorrhage	1		2	3
Atelectasis			2	2
<i>Adrenals.</i> —				
Focal necrosis		2	4	6
<i>Pancreas.</i> —				
Focal necrosis		4	1	5
<i>Serous Cavity.</i> —				
Pericardial effusion			6	6
Pleural effusion		5	6	11
Abdominal ascites			5	5

noted in the three series in all respects except renal pathology. The renal lesions in our series were classified according to Way's concept, but unfortunately no description of the kidney lesions accompanied Acosta-Sison's data.

Pathologic changes were most frequent in the liver, kidney, and lung, but were also commonly noted in the heart and brain. The high incidence of hepatic and renal lesions noted at autopsy is out of proportion to the number of deaths attributed to hepatic and renal failure on clinical grounds. The predominance of cerebral involvement as a cause of death in the clinical summary is not supported by anatomic evidence of cerebral injury in the cases seen at autopsy.

On the basis of these observations it appears that the pathologic lesions of toxemia involve many (if not all) organs of the body. Furthermore, the lesions produced are fundamentally the same in all cases, namely, focal areas of hemorrhage and necrosis.

### Comment

On the basis of clinical findings, it would appear that deaths from toxemia are almost always attributable directly to cerebral disorders, pulmonary edema, and renal failure. In contrast, the postmortem findings reveal a wide variety of lesions indicative of the complexity of toxemia. Many of the anatomic lesions which did not appear to be responsible for the patient's death were doubtless contributing factors.

Vasospasm is a consistent feature of toxemia.<sup>6, 7, 8, 9</sup> Many of the clinical signs and pathologic lesions are secondary to the anoxia produced by vasospasm. Quantitatively, these effects are proportionate to the severity and duration of the spasm. Time plays an important role in the production of anatomic lesions. As Acosta-Sison<sup>4</sup> pointed out, the fulminating case which comes to autopsy may show nothing but cloudy swelling of the parenchymal cells in the kidney and liver.

Recent evidence indicates that in some of the severe forms of eclampsia a substance similar to thromboplastin is liberated into the maternal blood stream, causing deposition of fibrin throughout the small vessels of the body.<sup>10</sup> However, similar lesions are not found in uncomplicated cases of toxemia which come to autopsy.

### *Cerebral Disturbances.*—

According to Dieckmann,<sup>11</sup> massive cerebral hemorrhage is not common in toxemia of pregnancy. Sheehan<sup>12</sup> reported that approximately one-third of the patients who die from eclampsia exhibit macroscopic evidence of hemorrhage in the brain, and a high incidence of small focal hemorrhages and necrosis has been noted by others. Thirteen of the cases in our series had a complete autopsy, including the brain; massive intracranial hemorrhage was present in five of these.

Cerebral hemorrhage occurs as the result of localized anoxia. This may be produced by vasospasm, primary thrombosis or embolism, circulatory failure, arteriosclerosis, and venous stasis due to edema or tumor of the surrounding



tissue.<sup>13</sup> As elsewhere in the body, the extent of the hemorrhage and subsequent tissue destruction will depend upon the severity and duration of the predisposing factors.

The 73 deaths which occurred during a convulsion are of extreme interest. We have been unable to find any satisfactory explanation for this type of death in the literature. Unfortunately, autopsy was not performed in any of our cases. The patients apparently died of respiratory paralysis, and it seems reasonable to assume, in view of the rapid death, that anoxia of the respiratory center occurred, with or without hemorrhage. The group of patients who died in coma, with or without antecedent convulsions, presented essentially the same problem, since autopsy examination was again lacking. Both Sheehan and Dieckmann have pointed out that coma and convulsions are not always due to eclampsia.

#### *Pulmonary Edema.—*

The problem of pulmonary edema is even more complex. An increase in cardiac output is one of the physiologic changes of pregnancy, and it has been well established<sup>14-17</sup> that this output is further increased during toxemia. No specific electrocardiographic changes have been reported in toxemic patients, but autopsy studies on such patients reveal lesions such as petechial hemorrhage, focal necrosis, and edema. While these changes do not as a rule appear to be sufficient to account for cardiac failure, it is possible that the combination of an increased cardiac load and minor organic injury to the heart may be enough to produce acute left ventricular failure with pulmonary edema.

In 18 per cent of the patients in our series who died from pulmonary edema, a precipitous drop in blood pressure, with a slow, weak pulse, preceded the clinical appearance of pulmonary edema. Adair,<sup>18</sup> reporting 26 similar cases, emphasized the importance of trauma as a factor in this condition. All but two of our patients developed this syndrome during or immediately following a traumatic delivery. In the other two cases the shock and pulmonary edema followed a convulsion.

#### *Renal Dysfunction.—*

Severe disturbances of renal function were more common in our series than in most of those which have been reported. Thirty deaths were attributed to renal failure, and in 44 additional cases severe oliguria or anuria was recorded, although it was not considered the immediate cause of death.

In recent years considerable attention has been devoted to the pathology of the kidney in toxemia and related complications.<sup>12, 19</sup> Although there is some difference of opinion regarding the nature of renal lesions it is generally agreed that they are secondary to circulatory impairment with consequent tissue destruction. The renal lesions vary from small focal areas of necrosis to nearly complete destruction of the cortical regions of both kidneys. Whether these differences are qualitative or quantitative is not certain. The difference may depend upon whether there are merely local areas of vasospasm within the

cortical regions or whether the cortical circulation is shunted in the manner described by Trueta.<sup>20</sup> Mild degrees of destruction of the renal parenchyma are reversible.

Impairment of the excretory function of the kidney leads to uremia and its functional consequences. The majority of the patients whose deaths were attributed to this condition slowly became comatose and died. However, in a few who were rather vigorously treated with fluids severe pulmonary edema developed prior to death. It is impossible to evaluate the precise role of renal suppression in the fatal outcome of the 44 cases in which death occurred during the acute phase of toxemia.

#### *Hepatic Failure.—*

The classic picture of hepatic failure is rarely seen in toxemia of pregnancy. A previous review<sup>21</sup> of the 1,500 maternal deaths analyzed by the Committee on Maternal Welfare revealed that liver damage may have contributed to the fatal result in 14 cases. The general pathology of the liver has been adequately described by Himsworth,<sup>22</sup> who pointed out the multiplicity of factors which may injure the parenchymal cells of the liver. These factors include nutritional deficiency, acute toxemia, congestive failure, and certain drugs.

#### *Involvement of Other Organs.—*

Extensive destruction of other organs, such as the pituitary gland, the adrenals, and the pancreas, may alter the physiology of the toxemic patient to such an extent that survival is impossible. The Sheehan syndrome represents the end result of such physiologic alterations. Disturbance of the relationship between the pituitary and the adrenal glands may account for the extreme sensitivity of these patients to trauma of any sort.

### **Summary**

Analysis of 1,500 maternal deaths which occurred in North Carolina during the period of six and one-half years revealed that toxemia was directly responsible for 393 fatalities, and contributed to an additional 140. Clinically it appeared that cerebral disturbances, pulmonary edema, or renal suppression was the immediate cause of death in almost all cases. Autopsies performed in 21 cases revealed focal necrosis and hemorrhage in many organs, but principally in the liver, kidneys, lung, heart, and brain. These findings emphasize the complexity of toxemia and indicate the need for consideration of the patient as a whole in the treatment of this condition.

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## THE EFFECT OF OXYTETRACYCLINE IN PREGNANCY COMPLICATED BY GLOMERULAR NEPHRITIS: A CASE STUDY\*

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IT HAS been previously reported from this laboratory that penicillin and oxytetracycline (OTC or Terramycin) afford complete protection to rats against a lethal dose of menstrual toxin, an effect which cannot be attributed to the bactericidal properties of these antibiotics.<sup>1</sup> The albuminuria and edema that develop in the test animals during the first 18 hours after the subcutaneous injection of a lethal dose of sterile menstrual discharge disappear if either of these drugs is simultaneously administered, rather than becoming progressive and terminating in death at 24 to 48 hours. Subsequent experiments upon women with pre-eclampsia or eclampsia revealed that toxic signs and symptoms were alleviated in response to these drugs, the most clear-cut effects being reduced albuminuria and an increased urinary output of fluid and electrolytes.<sup>2, 3</sup> In experiments on 3 nonpregnant women, 2 with chronic renal disease, an increased output of sodium and potassium was likewise observed but without any demonstrable changes in albuminuria or fluid balance.<sup>3</sup> Three of the 13 pregnancies reported were in patients with chronic renal disease. In 2 of them penicillin or Terramycin administration was started at the first sign of superimposed toxemia, as evidenced by a rise in the 24-hour output of urinary protein. The hope was that by controlling toxic signs from the start a more normal development of placental function might be possible in these women for whom the obstetrical prognosis is so very poor. In these 2 cases this end appeared to be accomplished, since the urinary output of the sodium pregnanediol glucuronide complex, a gauge of placental function,<sup>4</sup> rose as albuminuria fell and continued to rise till pregnancy advanced to a stage where a healthy infant could be delivered and survive. The object of the present communication is to present a detailed study throughout pregnancy on another such patient. The experiment was designed to learn as much as possible under controlled conditions concerning the action of OTC in this situation.† From the clinical point of view the experiment was not successful, since placental function failed to develop and the 2 pound, 8 ounce

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†Oxytetracycline for this experiment was gratuitously supplied by Chas. Pfizer & Co., Inc.



infant delivered by section at 34 weeks did not survive. As a fundamental investigation into possible mechanisms involved in the influence of OTC upon albuminuria and fluid and electrolyte balance, however, the results have been informative and quite conclusive so far as they go. This information is presented in detail in the figures. It will be briefly summarized in the text but no attempt at any interpretation of the findings will be made at this time.

### Methods

Each urine specimen was kept cold during the period of collection and analyzed on the day the collection was completed. Creatinine and creatin were measured by use of the Jaffé reaction as originally described by Folin<sup>5</sup> but adapted to the use of a spectrophotometer. Urinary protein was quantitated by the spectrophotometric measurement of turbidity after precipitation with sulfosalicylic acid, always with a urine blank, as is especially necessary when the urines contain OTC.<sup>3</sup> Serum proteins were assayed by the biuret method as described by Lever and associates,<sup>6</sup> serum albumin by methanol precipitation as described by Christenson,<sup>7</sup> and nonprotein nitrogen by Nesslerization. Sodium and potassium of the urine and serum were assayed on the Barclay flame photometer with an internal standard. Serum chlorides were done by iodometric titration as described by Van Slyke and Hiller.<sup>8</sup>

The endogenous creatinine clearance was used in approximating the rate of glomerular filtration with full realization of the shortcomings of such a method in a patient with chronic renal disease. Clearance periods ranged from 3 hours to 24 hours with a single blood sample being taken for serum creatinine during each clearance period. In the case of 24-hour periods, particularly when the patient was in the hospital, the dietary creatinine was not believed to fluctuate enough to produce significant changes in the day-to-day serum creatinine concentration. The glomerular filtration rate as estimated by the endogenous creatinine clearance allows for the calculation of the total amount of electrolyte filtered at the glomeruli during the clearance period. Such a calculation assumes that ionic Na and K are completely filtered from the serum and appear in the same concentration in the glomerular filtrate. The ratio of the amount of Na and K in the urine to the amount theoretically present in the glomerular filtrate during a clearance period represents that electrolyte which has escaped reabsorption by the renal tubules. Expressed as a percentage it has been found that during the last 10 weeks of pregnancy normal patients excrete only about 0.5 per cent to 1.0 per cent of the total amount of Na filtered at the glomeruli (C. C. R., unpublished observations).

The urinary sodium pregnanediol glucuronide complex (NaPG) was determined by the Venning<sup>9</sup> method. Recovery of pregnanediol itself, in HCl hydrolyzed aliquots of urine, was performed in duplicate by our<sup>10</sup> modification of the Sommerville, Gough, and Marrian procedure. The NaPG complex is calculated as pregnanediol and always gives higher figures than those for pregnanediol only, as would be expected, since it is known to contain at least two products of progesterone other than pregnanediol.<sup>4</sup> The difference between these two values, the "x" steroid figure, appears to provide a valuable gauge of progesterone metabolism, rising values as pregnancy progresses being associated with evidence for normal metabolism and utilization of progesterone, and vice versa.<sup>4</sup>

### Explanation of Figures

In Figs. 1 through 5 the results of analysis on 24-hour urine specimens are graphed, solid bars representing days when no OTC was being administered,

INFLUENCE OF TERRAMYCIN ON URINARY PROTEIN AND SERUM NON-PROTEIN NITROGEN

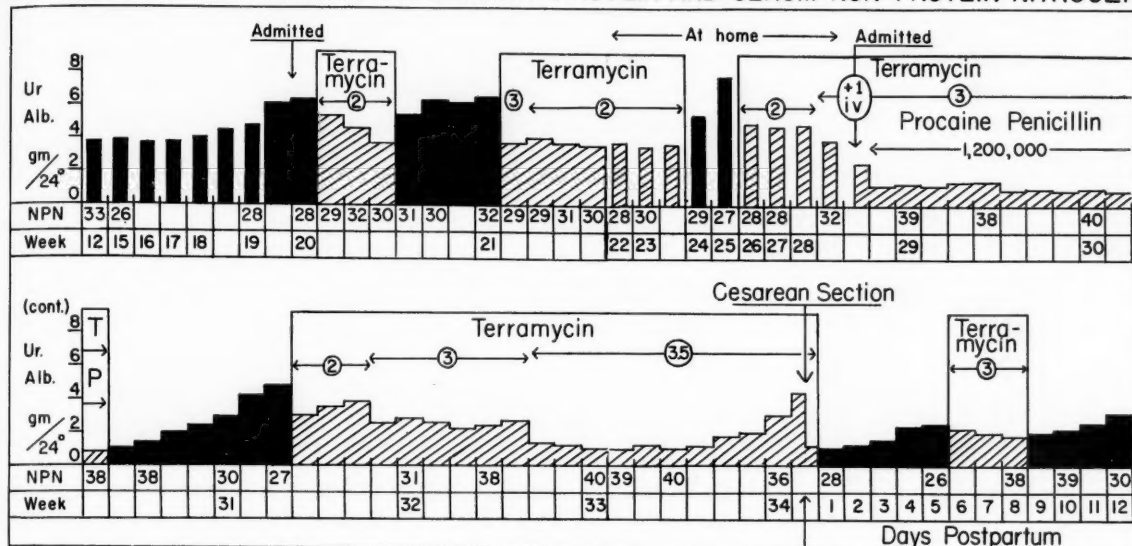


Fig. 1.

INFLUENCE OF TERRAMYCIN ON URINARY CREATIN AND SERUM PROTEINS

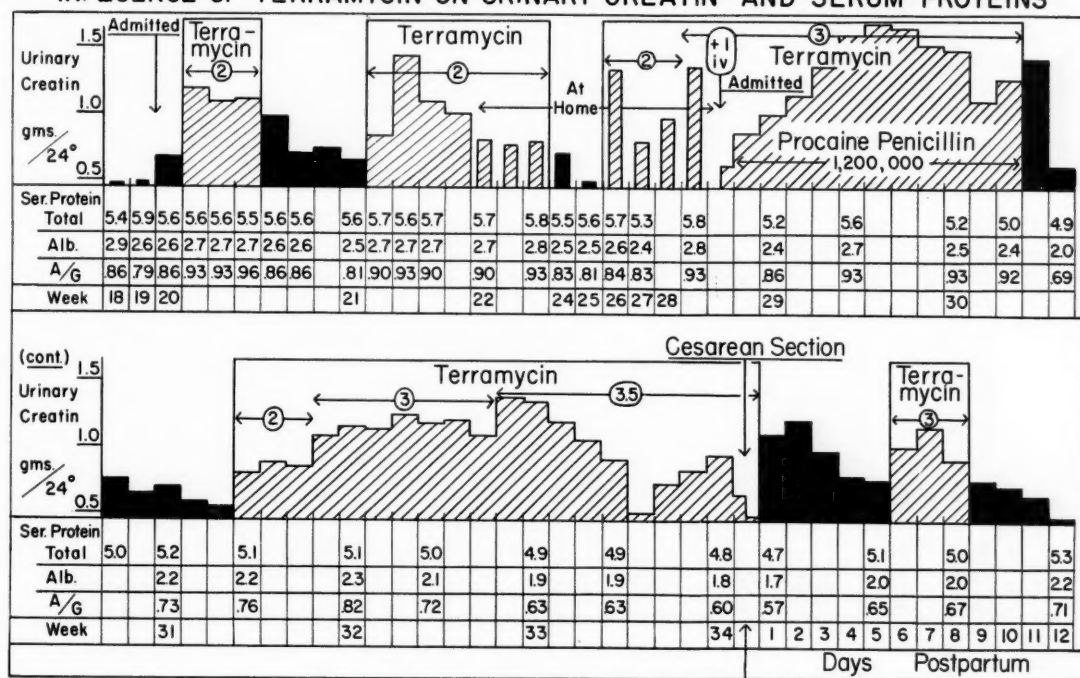


Fig. 2.

and cross-hatched bars depicting days on which the patient received the drug. The digits in circles show the dosage of OTC in grams per 24 hours, with arrows denoting the period of administration. At the start of each experimental period 0.5 Gm. of Terramycin was given intravenously in 25 ml. of 5 per cent glucose. Otherwise (except where indicated at 28½ weeks)

Terramycin was taken by mouth in divided doses between 8 A.M. and 10 P.M. Bars separated by spaces represent individual 24 hour specimens, most of which were collected while the patient was at home. Bars joined to one another represent consecutive daily specimens, all of which were collected in the hospital. The results of serum analyses are given below the graphs. Sodium, potassium, and chlorides are expressed in milliequivalents per liter

### INFLUENCE OF TERRAMYCIN ON POTASSIUM OF URINE AND SERUM

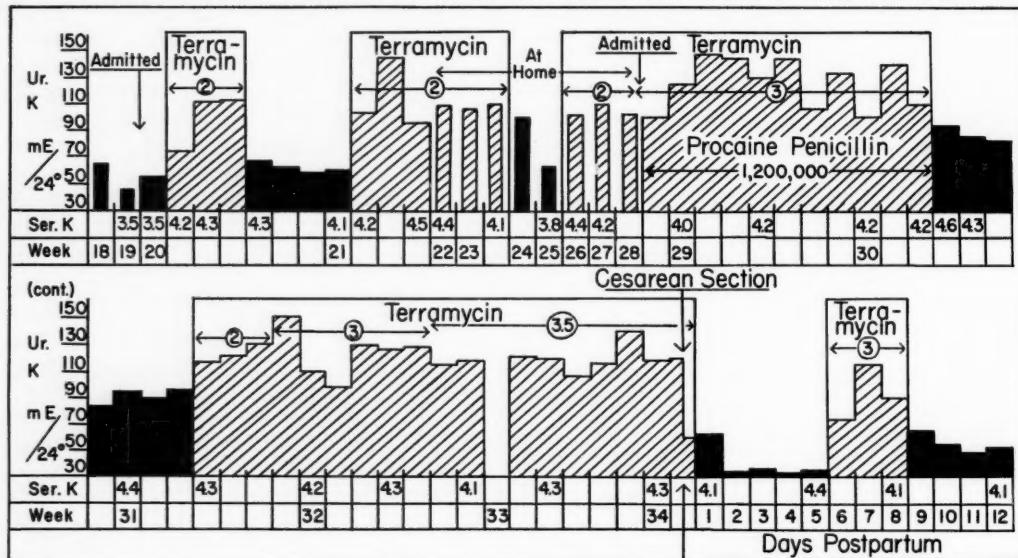


Fig. 3.

### INFLUENCE OF TERRAMYCIN ON URINARY SODIUM, FLUID BALANCE, AND Na AND Cl OF SERUM

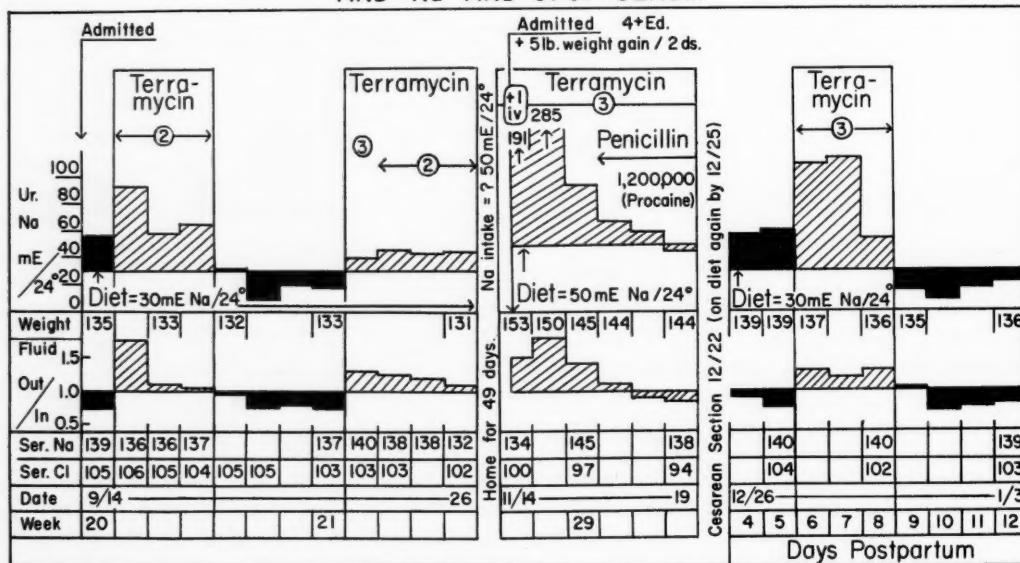


Fig. 4.

of serum, nonprotein nitrogen in milligrams per cent, total protein and serum albumin in grams per cent. Fasting blood was collected for all analyses, at 8 A.M. when the patient was in the hospital and somewhat later in the morning when she was being seen in the clinic.

### INFLUENCE OF TERRAMYCIN ON TUBULAR RESORPTION OF ELECTROLYTES

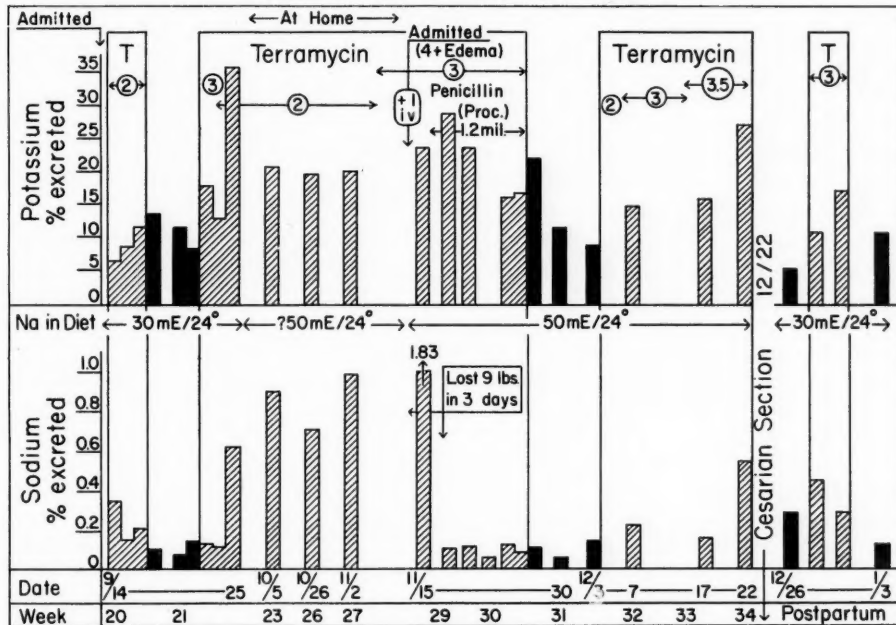


Fig. 5.

### URINARY METABOLITES OF PROGESTERONE AS RELATED TO ALBUMINURIA

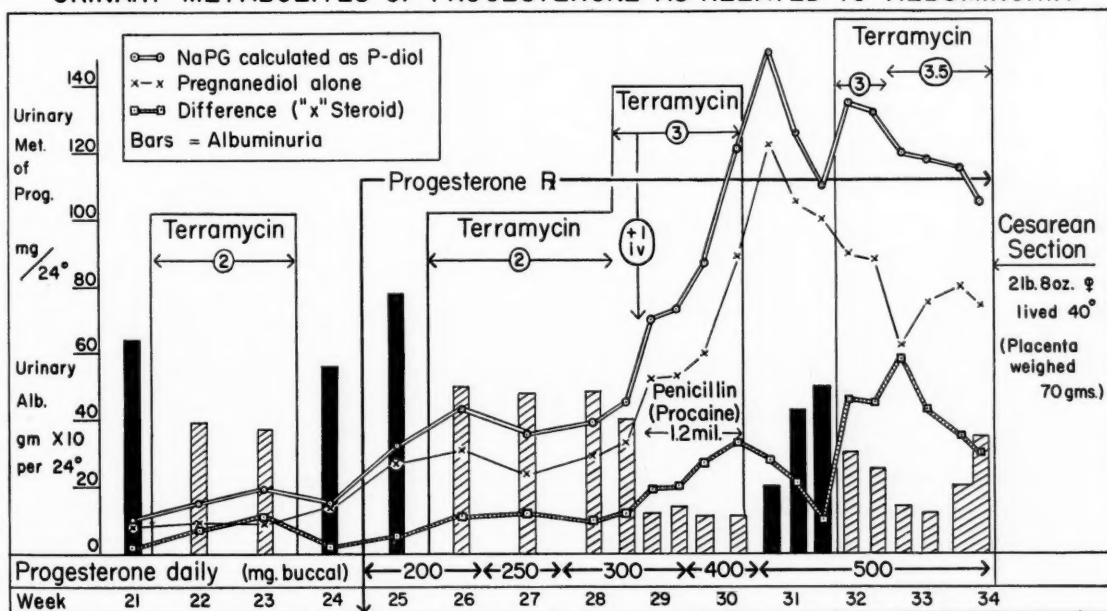


Fig. 6.



In Fig. 6 the results of analyses for progesterone metabolites are given, together with the urinary protein content of each 24 hour specimen that was analyzed for the NaPG complex and for pregnanediol alone. The same system of solid and cross-hatched bars is used for depicting albuminuria. For the sake of clarity, bars were not used for depicting progesterone metabolites, the individual assays being joined by lines to show the curves of excretion.

### Presentation of Case and Experimental Results

Mrs. M. D., aged 28 years, gravida iii, was registered at the prenatal clinic of the Boston Lying-in Hospital on July 9, 1953, when she was 10 weeks pregnant. She gave a history of scarlet fever and rheumatic fever in childhood and "kidney trouble" since marriage in 1948. Her first pregnancy, in 1949, terminated in spontaneous delivery, at 28 weeks, of a 2 pound, 11 ounce living infant. Albuminuria had been discovered early in that pregnancy and a diagnosis of chronic glomerular nephritis with pyelitis made. The last month was complicated by severe superimposed pre-eclampsia. Interruption of pregnancy by cesarean section had been scheduled for the day after she spontaneously went into labor. In 1950, at 12 weeks' gestation, therapeutic abortion was performed at this hospital because of an acute flare-up of her chronic glomerular nephritis.

At her first prenatal visit in the present pregnancy she had 4 plus albuminuria and was admitted for evaluation. The urinary sediment of a catheter specimen contained fine granular casts with rare red blood cells per high-powered field, 10 to 15 white blood cells, and no bacteria. The intravenous pyelogram was normal. A urea clearance test, with a flow of 2.5 ml. per minute, revealed a maximum clearance of 70 per cent of normal. Blood chemistry was essentially normal except for an albumin-globulin ratio of only 0.96. Her blood pressure was normal and remained so throughout this pregnancy. It was decided that she was in a nephrotic stage of chronic glomerular nephritis. Interruption of pregnancy, because of the poor prognosis, was advised but was decided against because of the patient's strong desire to continue. She was started on the Smith and Smith stilbestrol regime at 11 weeks and told that she must come to the toxemia clinic once or twice weekly throughout the rest of her pregnancy, bringing with her each time a 24 hour specimen and an accurate record of her fluid intake during the period of collection. Careful instructions were given her as to how this should be done and she proved to be an extremely intelligent and cooperative patient in this respect. The constancy of her 24 hour output of creatinine throughout pregnancy bore witness to this, as did also the close correlation between weight and fluid balance. At 12 weeks she was put on a low-salt, high-protein diet. Salt restriction was not followed too conscientiously by her except during her hospital stays, as evidenced by the sodium content of her urine specimens.

From the twelfth to the eighteenth weeks of gestation, her output of urinary protein remained constant at 3.7 to 4.0 Gm. per 24 hour volume and there was no evidence of fluid retention. During the next 10 days, however, albuminuria rose rapidly to 6.3 Gm. per 24 hours (Fig. 1). There were no signs or symptoms of pyelitis associated with this rise. The urinary sediment of a catheter specimen contained red blood cells (3 to 4 per high-powered field) and casts, but only rare white blood cells and no bacteria. At 20 weeks she was admitted to the hospital for a study of the influence of Terramycin. At no time during the remaining course of her pregnancy was there any evidence of kidney infection.

*First hospital admission (20 to 20½ weeks gestation):* During this twelve-day hospital stay each voiding of urine (collected and accurately timed by the patient herself) was analyzed separately in order to follow diurnal rhythms. These were apparent in the values for urinary protein, potassium, creatin, and creatinine, with peaks in the excretion rates of all four in the late afternoon or early evening, and low levels in the early morning hours. There was no diurnal rhythm in sodium output. Only the 24 hour values for these constituents are shown in the figures, since they clearly illustrated the influence of OTC. After 24 hours of observation without treatment, Terramycin administration was begun. Between September 15

and September 26, 2 Gm. was given daily for 3 days, omitted for 4 days, and given again for 4 days. Coincident with its administration the following changes were observed: lowered albuminuria (Fig. 1), increased creatinuria (Fig. 2), and a rise in the albumin-globulin ratio of serum proteins (Fig. 2), increased urinary output of potassium with a suggestive rise in serum potassium (Fig. 3), and diuresis accompanied by weight loss and a negative sodium balance (Fig. 4). A decreased tubular resorption of electrolytes while OTC was being given was indicated by rises in the percentage excretion of the sodium and potassium filtered through the glomeruli (Fig. 5). Since all of these changes were reversed during the 4 days when OTC was omitted, they appeared to be "post hoc." There were no significant changes in serum nonprotein nitrogen (Fig. 1) or the sodium or chloride of the serum (Fig. 4) during this period of observation. Analyses at the twenty-first week for urinary sodium pregnanediol glucuronide (the NaPG complex) and for free pregnanediol revealed only 10 mg. of the former and 8 mg. of the latter per 24 hour volume (Fig. 6). These are very low figures for 21 weeks' gestation.

*Home for 49 days (21½ to 28½ weeks gestation):* The patient was discharged from the hospital on 2 Gm. of Terramycin daily and dietary instructions.\* She was seen at the clinic 2 days later and at weekly intervals thereafter through November 11, 28½ weeks. Two grams of OTC was taken daily for 2 weeks, omitted for 10 days, and taken again for 2½ weeks. At no time was there any diarrhea or intestinal disturbance on this dosage. At 24 and 25 weeks, when no OTC was being taken, the following changes were observed: a rise in proteinuria from 3.7 to 7.8 Gm. per 24 hours (Fig. 1), a drop in creatin output from 0.78 to 0.49 Gm. per 24 hours (Fig. 2) and in A-G ratio from 0.93 to 0.81 (Fig. 2), a decrease in urinary potassium from 110 to 63 meq. per 24 hours and in serum potassium from 4.1 to 3.8 meq. per liter (Fig. 3). Sodium output during this interval is not graphed because of the extremely variable figures while the patient was at home where her dietary intake could not be controlled. No observations were made on creatinine clearance for the study of tubular resorption of electrolytes during these 10 days when therapy was omitted. Her ratio of fluid output to intake decreased, however, and she gained 4¾ pounds between the twenty-fourth and the twenty-fifth weeks of gestation.

At 22 and 23 weeks, while taking OTC, the urinary output of "x" steroids (that is, progesterone metabolites other than pregnanediol) increased slightly (Fig. 6), indicating more normal metabolism of available progesterone.<sup>4</sup> There was no increased output of pregnanediol itself, however. At 24 weeks, when no Terramycin was being taken, a marked drop in "x" steroid was noted. This patient's 24 hour excretion of progesterone metabolites was extremely low for this period of gestation and not rising normally despite the fact that she had been on steadily increasing dosages of stilbestrol since the eleventh week. It was feared that her pregnancy would not continue unless her placental inadequacy was replaced by the giving of progesterone. The administration of buccal Proluton† was instituted and continued throughout the rest of pregnancy in the dosages shown in Fig. 6.

Reinstitution of OTC therapy at 26 weeks was accompanied by a reversal of all the changes observed upon its omission. On 2 Gm. daily, however, urinary protein was lowered only to 5.0 Gm. per 24 hours. Upon the dose being increased to 3 Gm. daily albuminuria dropped further, but the patient for the first time complained of nausea and vomiting from the drug. Two days after the clinic visit in which this complaint was registered she was admitted to the hospital with pitting edema of the legs, arms, and face, blurred vision, headache, and a blood pressure of 128/88. Her blood pressure readings up to this time had been 104 to 120/60 to 80. She had gained 5 pounds in 2 days.

\*To the usual toxemia diet No. 3 of the Boston Lying-in Hospital (30 meq. Na daily) a quart of milk was added. This increase in sodium intake to 50 meq. daily was deemed advisable because of our unpublished experience in 2 toxemic patients to whom Terramycin was given over long periods of time. Both were on the Boston Lying-in Hospital toxemia diet No. 1, which restricts sodium to 250 mg., or only 11 meq. daily. Both developed symptoms suggestive of sodium depletion together with low serum sodium (128 meq. per liter), a situation that was corrected by increased sodium intake.

†Buccal Proluton, 50 mg. progesterone per tablet, was gratuitously supplied for this experiment by the Schering Corporation.

*Second hospital admission (28½ weeks to delivery at 34 weeks):* The patient was admitted on September 14 at 7 P.M. She had felt too sick to take any of her medication for the past 24 hours. Between 7 P.M. and midnight two 0.5 Gm. doses of Terramycin were given intravenously, each in 25 ml. of 5 per cent glucose, and 1 Gm. was taken by mouth. By seven o'clock the next morning she had excreted 2,200 ml. of urine and lost 3¼ pounds in weight. Her symptoms had disappeared and her blood pressure was 110/70. During the next 24 hours, on 3 Gm. of OTC by mouth, she excreted 5,400 ml. of urine and lost another 5 pounds in weight. This rapid diuresis was accompanied by a tremendous output of urinary sodium (Fig. 4), a significant drop in serum chlorides (Fig. 4), and evidence of a very marked decrease in tubular resorption of sodium (Fig. 5). The patient felt well, had a good appetite and no more nausea or vomiting. For the following 11 days procaine penicillin, 1,200,000 units daily, as well as Terramycin, was administered. This was accompanied by a marked lowering of albuminuria (Fig. 1), a rise in blood non-protein nitrogen (Fig. 1), an increase in creatin excretion to the very high figure of 1.7 Gm. per 24 hours (Fig. 2), and a prolonged high output of urinary potassium (Fig. 3). After 3 to 5 days on this regime she began complaining of muscular weakness and loss of appetite. Her sodium output decreased but this may have been due to lowered intake. There was no weight gain or fluid retention. Tubular resorption of potassium, as reflected by a high percentage excretion (Fig. 5) remained low. That of sodium appeared high, but here again the loss of appetite may have been involved, since she was not drinking her full quota of milk, the source of most of her dietary sodium. Because of increasing weakness and an episode of complete flaccidity at 30 weeks, together with the high urinary output of potassium, hypokalemia was suspected. An electrocardiogram, however, provided no evidence for this. Terramycin and penicillin were both discontinued, since the episode appeared to be clearly associated with their administration.

During this time when proteinuria was so markedly lowered, the urinary output of progesterone metabolites (Fig. 6) rose very rapidly. From 26 to 28½ weeks, despite two increases in the daily dose of buccal progesterone, there had been no increase in NaPG or pregnanediol. At 29 weeks, however, coincident with the pronounced lowering of albuminuria, and before any further increase in progesterone dosage, the output of both was greatly augmented, while the difference between the two, the "x" steroids, increased also. It is impossible to say, of course, how much of the large increment in urinary metabolites of progesterone observed at weeks 29 to 30½ was derived from administered progesterone. It almost seems, however, that a sudden "spurt" in placental secretion must have accounted for some of it. One wonders if there was some connection between this and the very high output of creatin at 29 to 30 weeks, since creatinuria is normal only in pregnancy and in growing children. The muscular weakness at this time, however, reminds one of the creatinuria that accompanies progressive muscular dystrophy.

For 7 days, at 30½ to 31½ weeks' gestation, no antibiotics were given. The patient regained her strength and appetite. Albuminuria rose from 1.0 to 5 Gm. daily (Fig. 1), blood nonprotein nitrogen dropped back to normal (Fig. 1), creatinuria decreased (Fig. 2), the A-G ratio fell (Fig. 2), potassium output was lowered (Fig. 3) with decreased percentage excretion of potassium and continued low percentage excretion of sodium (Fig. 5), and the output of progesterone metabolites fell with a pronounced decrease in "x" steroids (Fig. 6). All of these changes, except for the drop in pregnanediol (Fig. 6), were reversed upon reinstitution of Terramycin therapy. No significant rise in blood non-protein nitrogen (Fig. 1) occurred until 3 Gm. daily was given. Between the thirty-second and the thirty-fourth weeks the A-G ratio (Fig. 2) fell steadily despite the lowered albuminuria. During the last week before delivery albuminuria began to rise despite the daily intake of 3.5 Gm. of OTC. The NaPG values had been dropping (except for a temporary increase when Terramycin therapy was first reinstituted) for 3 weeks. An increased output of pregnanediol itself, such as has been frequently observed just prior to accidents in late pregnancy,<sup>4</sup> was in progress. Because of these changes and the hearing of rapid fetal heart sounds (160 per minute) on the morning of December 22, it was decided to interrupt the pregnancy by cesarean section. This was done under local

anesthesia at noon on that day. The 2 pound, 8 ounce infant exhibited chest retraction from the start and died of atelectasis forty hours later. The placenta weighed only 70 grams. The pathological diagnosis was prematurity with relative postmaturity; that is, the "Tenney changes," or premature senility of the syncycial trophoblast which is associated with progesterone secretion.

*Days 1 through 12 post partum:* An inlying catheter was inserted at delivery so as not to interrupt urine analyses which were continued throughout the patient's hospital stay. For 3 days, days 6 through 8 post partum, 3 Gm. of OTC was given daily. The results of this experiment differed from those performed during pregnancy in two respects: there was no significant lowering of albuminuria (Fig. 1) or rise in the A-G ratio of serum proteins (Fig. 2). Increased creatinuria (Fig. 2), increased output of sodium and potassium (Figs. 3 and 4), associated with decreased tubular resorption (Fig. 5) and a rise in blood nonprotein nitrogen (Fig. 1) were all observed, and these changes were reversed during the last 4 days when no OTC was given.

### **Harmful Effects From Oxytetracycline**

The pregnant patients whom we have studied while taking Terramycin have been remarkably free from the intestinal disturbances frequently observed upon its oral administration. Instructions have been given that each dose be taken with milk. Its prolonged administration has been accompanied by sufficient milk consumption to bring the total sodium intake to no less than 1.2 Gm. daily (see footnote p. 197). The subject of this investigation had no complaints while on 2 Gm. of OTC a day (weeks 20 to 28 of gestation). Upon increasing the dose to 3 Gm. at 28 weeks, she had nausea and vomiting for a short period, but this disappeared without reducing the amount given and she at no time had any diarrhea. The episode of muscular weakness at 29½ to 30½ weeks was associated with combined Terramycin and penicillin therapy. In commenting upon it in presenting the case, we pointed out that the only objective finding to account for it was very marked creatinuria. Reinstitution of therapy with OTC alone, in daily dosages increasing from 2 to 3.5 Gm. (weeks 31½ to 34), was accompanied by no recurrence of symptoms.

On 3 or 3.5 Gm. of OTC daily there was a rise in serum nonprotein nitrogen to 39 or 40 mg. per cent (Fig. 1). This was clearly associated with doses of the drug in amounts greater than 2 Gm. daily. Bateman and associates<sup>11</sup> have reported very high values for blood nonprotein nitrogen and blood urea nitrogen in patients with advanced cancer who died while receiving intensive intravenous therapy with OTC. Values for blood nonprotein nitrogen of 100 to 300 mg. per cent were recorded without any anuria or oliguria. In only 3 of the 7 cases autopsied were there diseased kidneys and no postmortem changes were found that were common to all. Sedwitz, Bateman, and Klopp<sup>12</sup> studied the effect of intravenously administered OTC in dogs, giving large enough doses to produce high levels of circulating OTC, as had been observed in the cases reported in human beings. High nonprotein nitrogen and urea were again observed in the blood, and death ensued. No abnormality of the kidney was found to account for death and Bateman<sup>13</sup> has since demonstrated conclusively in nephrectomized animals that the rise in blood nonprotein nitrogen does not reflect kidney damage.



There was no evidence for kidney damage from OTC in the subject of this investigation. All of the findings pointed to improved renal function as a result of administration of the drug, namely, reduced albuminuria with a rise in serum A-G ratio, diuresis, and increased excretion of electrolytes with decreased tubular resorption. A urea clearance test on July 23, 1953, before OTC had been given, showed maximum clearance of 70 per cent of normal with a blood urea nitrogen level of 11 mg. per cent and a flow of 2.5 ml. per minute. This test was repeated on Dec. 17, 1953, when the patient was 33½ weeks pregnant. She was then receiving 3.5 Gm. of OTC daily and had been taking the drug uninterruptedly for 15 days. Maximum clearance was 106 per cent of normal with a blood urea nitrogen level of 15 mg. per cent and a flow of 5.3 ml. per minute. A urine concentration test and a test for the rate of excretion of phenolsulfonphthalein were also done at this time. The former showed good concentration (specific gravity of 1.020) and the latter normal excretion (45 per cent of the dye in 30 minutes and 60 per cent in one hour). On the twelfth postpartum day, after no OTC for 4 days, urea clearance was again tested and showed essentially the same result as had been observed in July before OTC was started, that is, 74 per cent of normal. The level of blood urea nitrogen had dropped from 15 to 10 mg. per cent, indicating that blood urea nitrogen as well as blood nonprotein nitrogen had been elevated during Terramycin therapy. We could find no indication that this reaction to the drug reflected any type of kidney damage.

### Comments

Any interpretation of the findings in this case must await further investigation. Our original basis for trying penicillin and OTC in toxemia of pregnancy was the discovery that these two drugs were remarkably effective in neutralizing the toxic response of rats to sterile menstrual discharge.<sup>1</sup> This, together with our evidence that late pregnancy toxemia was a menstruation-like phenomenon,<sup>14</sup> made the investigation of their influence upon toxemia logical. The alleviation of toxic signs and symptoms observed<sup>2, 3</sup> was in keeping with the idea that penicillin and OTC either neutralized the effect or caused the rapid elimination of toxic products of tissue catabolism. The finding that OTC increased the urinary output of sodium and potassium in non-pregnant patients who had no known source of "toxin,"<sup>3</sup> however, complicated the picture. The additional findings herein presented, that a rise in blood nonprotein nitrogen and an increased output of urinary creatin, not only during pregnancy but in the postpartum period, result from what appear to be completely nontoxic doses of OTC, make further investigation imperative. Nitrogen balance and other nitrogenous constituents of blood and urine should be studied in relation to OTC administration. The possibility should also be investigated that all of the changes observed may be mediated by some effect on the endocrine system. It is difficult to conceive of any manner in which the bactericidal property of Terramycin could explain the results.

### Summary

To a pregnant patient with chronic glomerular nephritis oxytetracycline has been orally administered in doses of 2 to 3.5 Gm. daily for periods of 3 days to 5 weeks. Its administration was started when the patient began showing an increased output of urinary protein at 20 weeks' gestation, it having been ascertained that this increase was not associated with any infectious process. From the twentieth to the thirty-fourth weeks of gestation, when pregnancy was terminated, the influence of terramycin upon albuminuria, the urinary metabolites of progesterone, urinary creatin, potassium, sodium, and fluid balance, upon tubular resorption of electrolytes, and upon serum non-protein nitrogen, proteins, sodium, potassium, and chlorides was investigated. Terramycin therapy was periodically interrupted in order to be sure any changes observed were due to its administration. The experiment was repeated during the first 12 postpartum days. The following changes resulted from OTC administration during pregnancy: (1) decreased albuminuria and a rise in the albumin to globulin ratio of the serum; (2) increased creatinuria; (3) a rise in serum nonprotein nitrogen when more than 2 Gm. of Terramycin was given daily; (4) increased urinary output of potassium with a suggestive rise in the level of serum potassium and evidence for decreased tubular resorption of potassium; (5) diuresis at periods that had been preceded by fluid retention, with increased urinary output of sodium and evidence for decreased tubular resorption of sodium; (6) a change in the urinary metabolites of progesterone indicative of a more normal metabolism of available progesterone, and a marked increase in pregnanediol output coincident with a pronounced lowering of urinary protein.

During the postpartum period the changes in creatinuria, nonprotein nitrogen, and the urinary output of fluid and electrolytes were equally marked during OTC administration. Albuminuria and the A-G ratio of serum proteins, however, were not significantly influenced at this time.

We wish to acknowledge the technical assistance of Miss Agnes Currie and Miss Nora Nutt.

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## THE INCIDENCE OF POSTPARTUM HYPOPITUITARISM

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ONE of the most serious long-term sequelae of abnormal obstetrics is hypopituitarism. In comparison with it, such conditions as prolapse, stress incontinence, and pelvic adhesions are only minor local inconveniences. The obstetrician is very directly concerned, because the primary lesion in the pituitary occurs at the time that the patient is in his care, and he is thus the only person who can take steps to prevent it. Furthermore, if the obstetric conditions have been such that this primary lesion might possibly have occurred, it is important that he should inform the family doctor when the patient leaves the hospital so that any subsequent hypopituitarism can be diagnosed and treated early. On the other hand, during the subsequent years most of the patients do not bother to consult anyone about their amenorrhea, so that a gynecologist is likely to see only those cases referred to him by endocrinologists for investigation of the superinvolution.

The initial catastrophe occurs when the patient has severe blood loss or shock at about the time of delivery, the most common obstetric factors being retained placenta or postpartum hemorrhage. During the resultant general circulatory disturbance there is a specific arrest of the blood supply to the anterior lobe of the pituitary, which thus undergoes ischemic necrosis (infarction). In about half the cases the necrosis involves 95 to 98 per cent of the anterior lobe, sparing merely the pars tuberalis and a few tiny patches of subcapsular parenchyma. For all practical purposes this may be regarded as a complete loss of the anterior lobe; it is more than is usually produced by the other types of pathological lesions which affect the pituitary, or even by surgical hypophysectomy in human beings.

During the next few months the necrosed area heals to a small fibrous scar which remains unchanged for years afterward. The appearances in this healed stage can be seen in Figs. 1 to 10. These show a midline section through a block of tissue consisting of the hypothalamus, the pituitary, and the dura of the sellar region, removed in one piece. In some cases the anterior lobe is replaced by a mass of loose fibrillar tissue which retains the rough shape of the original gland; in the other cases this becomes condensed to a thin layer of fibrous tissue on the floor of the sella.

If the original necrosis involved more than about two-thirds to three-fourths of the lobe there will be some subsequent pituitary insufficiency; if it involved practically all of the lobe the subsequent insufficiency will be very

severe. The patient then continues as a chronic invalid for a long time, commonly 5 to 20 years, and finally dies in coma. There have been several recent accounts of the clinical course: Sheehan and Summers (1949); Farquharson (1950); Gamna and Ceresa (1950); Cook, Bean, Franklin, and Embick (1951); Perkins and Rynearson (1952); Hubble (1952); Leng-Levy and Burlaud (1952); Oelbaum (1952); Mahaux (1952); Wilson (1953); Lewis (1953); and Iannacone (1953). The last of these reviews contains a detailed analysis of the literature. The therapy has been discussed elsewhere (Sheehan and Summers, 1952 and 1954).

It is widely believed that postpartum hypopituitarism, though of obvious academic interest, is so rare that it is not of very much practical importance. The purpose of the present paper is to show that in fact it is not uncommon. The evidence will be summarized here under four headings, and finally a series of cases will be recorded to point the moral.



Fig. 1.

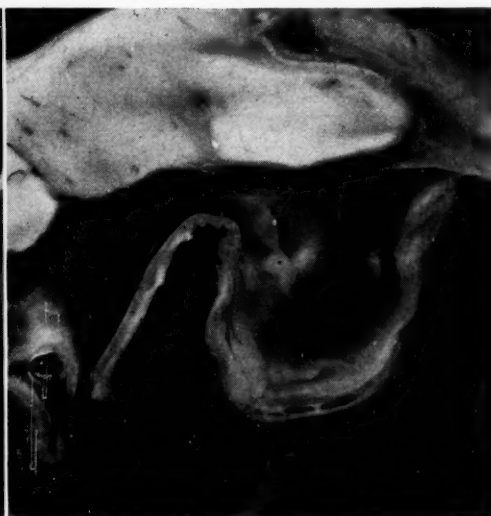


Fig. 2.

Fig. 1.—Shows a normal pituitary.

Fig. 2.—Shows the healed stage of a postpartum necrosis, with the anterior lobe represented only by loose fibrous tissue.

Figs. 1 to 10.—Midline sections of hypothalamus, infundibulum, pituitary, and dura of sellar region. In all sections, anterior is to the right. The white area above is the optic chiasma.

### **Incidence of Fresh Pituitary Necrosis at Autopsies in the Puerperium**

Patients with pituitary necrosis may die in the puerperium from the same causes as do other obstetric patients; there is no reason to believe that the lesion in the pituitary is fatal at this stage. In a series of autopsies on patients who died in the puerperium, some with and some without pituitary necrosis, there was always an adequate cause of death, such as puerperal sepsis or pulmonary embolism, quite unrelated to the pituitary necrosis (Sheehan, 1948).

Table I shows the number of cases with a fresh pituitary necrosis observed in that series; i.e., the necroses which had occurred at this particular



delivery. The data are restricted to autopsies on patients who died between 12 hours and 35 days post partum. This is because, though the necrosis usually begins at about the time of delivery, it does not become recognizable by ordinary histological methods until at least 12 hours later. The grades of hemorrhage and shock in this and Table II are assessed according to the clinical condition of the patient. "Severe" or "very severe" means that she was exsanguinated, comatose, and pulseless, and was considered to be almost moribund. "Moderate" means that she had usually had very severe hemorrhage and had a pulse rate over 140; she was restless and, though she usually remained conscious, she remembered nothing subsequently. It is to be emphasized that the significant point is the degree of "vasomotor collapse" or "shock" or "circulatory failure." The actual volume of blood lost is an important factor in the production of the disturbance of circulation, but it cannot be used as a direct measure of the severity of that disturbance.

TABLE I. INCIDENCE OF FRESH PITUITARY NECROSIS AT AUTOPSY IN PATIENTS WHO DIED 12 HOURS TO 35 DAYS POST PARTUM

DEGREE OF HEMORRHAGE AND/OR SHOCK AT DELIVERY	PITUITARY NECROSIS		
	NONE	SMALL OR MEDIUM	LARGE
None or trivial	92	0	0
Moderate	26	11	3
Severe or very severe	9	8	19

It will be seen from Table I that pituitary necrosis was present in about one-fourth of these puerperal deaths and in three-fourths of the patients who had had severe hemorrhage or shock at the delivery. The question naturally arises of how far the high incidence as observed in these autopsies on patients who happened to die in the puerperium may be taken as representative of the incidence of pituitary necrosis in those patients who survived the puerperium. It might perhaps be considered that a large necrosis could make the patient less capable of resisting other complications during the puerperium, and thus that the patients who survived the puerperium would be mainly those who had not suffered pituitary necrosis. By its nature this is a subject on which no direct evidence is available.

Certain conclusions can nevertheless be drawn from Table I. A patient who survived after having had *small* or *medium-sized* necrosis of the anterior lobe would not be expected to have subsequent clinical evidence of hypopituitarism. On the other hand, a patient with a *large* necrosis who survived the puerperium would certainly be expected to have subsequent symptoms either of partial or of severe hypopituitarism. Thus it may be calculated that, if the data in Table I are representative of the condition of the survivors, about 8 per cent of patients who had moderate hemorrhage at delivery and about 53 per cent of those who had severe or very severe hemorrhage should, if they continued to live for months or years later, develop clinical evidence of hypopituitarism during that time.

### **Incidence of Clinical Hypopituitarism Following Hemorrhage and Shock at Delivery**

The only direct way of ascertaining how far the calculations in the last paragraph are valid is to follow up a series of obstetric patients who had hemorrhage or shock at the delivery, and to find what percentage actually show evidence of pituitary insufficiency in the following years. A study along these lines was reported by Sheehan and Murdoch (1938). The essential findings are summarized in Table II. It will be seen that about 15 per cent of the survivors from moderate obstetric hemorrhage or shock and 40 per cent of the survivors from severe or very severe hemorrhage or shock had subsequent hypopituitarism. These findings are in rough agreement with the calculations made from Table I.

TABLE II. INCIDENCE OF SYMPTOMS OF HYPOPITUITARISM IN LIVE PATIENTS SOME YEARS AFTER DELIVERY

DEGREE OF HEMORRHAGE AND/OR SHOCK AT DELIVERY	SUBSEQUENT CLINICAL HYPOPITUITARISM		
	NONE	PARTIAL	SEVERE
None or trivial	90	0	0
Moderate	52	7	2
Severe or very severe	24	11	6

Some reservations are, however, necessary before accepting that the results of this follow-up give a true picture of the incidence of hypopituitarism.

A. The follow-up was made at a time when it was generally accepted that the symptoms of pituitary insufficiency were those of classical Simmonds's disease. The investigation had been in progress some time before it gradually became clear that the error was in the textbooks and not in the patients. The true syndrome had thus to be worked out during the course of the study, and the importance of certain aspects was not recognized as clearly as it would be today. Furthermore, the study of the cases was mainly clinical, as few biochemical tests were then available. Despite these difficulties it is believed that the observed incidence of hypopituitarism in the series was reasonably correct; all the patients classified as "severe" had complete amenorrhea, superinvolution, and the general signs and symptoms of serious pituitary insufficiency.

B. A more important problem is how far the cases actually studied were representative of the whole group originally collected for follow-up.

The investigation was begun by making out from the obstetric hospital records a list of patients, including in particular all those who had had serious hemorrhage or shock at the delivery. A letter was sent to them, asking them either to come to the hospital for examination or to write a short note about their state of health. Those patients with whom contact was thus established were then investigated. A number of patients failed to reply, or the letters were returned by the Post Office marked "Gone, no address." A second letter was sent to those patients who had failed to reply to the first one. Some, but

not all, of those who still failed to reply were visited at their homes. Those whom the Post Office had not located were not tracked any further.

Such a follow-up, while excellent for most other diseases, is not fully satisfactory in the search for cases of hypopituitarism. The reason is that, when a patient has severe pituitary insufficiency, she commonly develops the mentality of a patient with myxedema. Thus she is usually far too apathetic to

Fig. 3.



Fig. 4.



Fig. 5.



Fig. 6.

Figs. 3 to 6.—Examples of healed stage of postpartum necrosis showing the type in which the anterior lobe is represented by a layer of condensed stroma in the floor of the sella.

answer letters. In addition she goes out of doors very little and has no desire to make the journey to the hospital. In many cases the husband is understandably not very cooperative; he has had the burden of a dirty, lazy wife for several years, and is usually not aware that her psychological condition

is due to illness. As a result he has lost all interest in her welfare, and he may have left her. The children, who have been grossly neglected by their mother, are often quite callous about her fate. Sometimes the family has been dragged down financially and socially by the patient, and has moved to a poorer district without leaving any forwarding address. And sometimes the patient has died in hypopituitary coma.

Fig. 7.



Fig. 8.



Fig. 9.

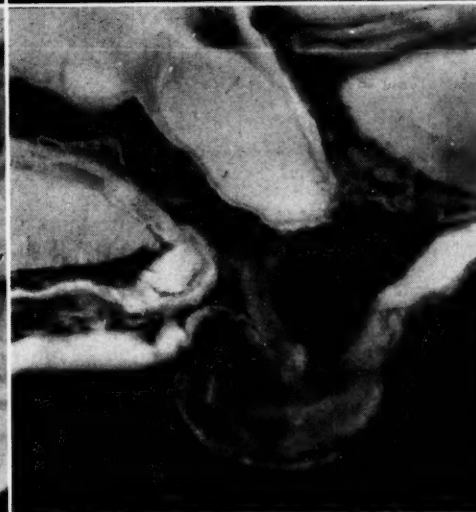


Fig. 10.

Figs. 7 to 10.—Examples of healed stage of postpartum necrosis, showing the type in which the anterior lobe is represented by a mass of loose stroma which occupies much of the sella.

Thus in practice the best method of follow-up of these cases of obstetric hemorrhage and shock is first to send a detailed questionnaire by post. A few patients who have had a postpartum necrosis may retain sufficient interest to reply to this, or their relatives may reply for them. But the great majority



of the patients who reply can be eliminated from further consideration as not having the mental and physical inertia which is characteristic of severe hypopituitarism. The main function of the questionnaire is to weed out these healthy patients. It is the patients who fail to reply who are most likely to have pituitary necrosis, and the real follow-up consists of visiting all of this group in their homes.

The follow-up recorded in Table II may thus be criticized on the grounds that it was not complete enough, so that it may have missed a number of the most severe cases of hypopituitarism. Nevertheless, even with this source of underestimation, the follow-up showed a very significant incidence of hypopituitarism.

### **Incidence of Identified Cases of Hypopituitarism in General Medicine**

The idea that hypopituitarism is very rare probably arises from the fact that most of the cases remain undiagnosed. This is due to several causes:

A. The patient does not bother to seek medical care. Her only concern is to keep warm and to be left undisturbed in her mental torpor and physical inertia.

B. If the relatives do get a doctor to see her, the conditions of the patient and of her home are not conducive to good medicine. In many of the severe cases the patient is dull and not sufficiently interested to discuss her symptoms. She makes only vague complaints about weariness and weakness and cold. Quite commonly she does not bother to mention any of the significant points in her history, such as that her illness began after a delivery at which she nearly died of hemorrhage, that she has had amenorrhea since then, and that she lost her pubic and axillary hair within the next couple of years. She is usually dirty and wearing too many clothes, and the house is in a state of neglect. In these difficult conditions even the best doctor is naturally discouraged from making a detailed investigation, and diagnosis easily gives place to symptomatic therapy. The doctor notices that she is pale so he prescribes iron and, when this proves to be without effect, he tries liver therapy. When this in turn is found useless, he notices that her face is rather puffy, her skin dry and her eyebrows thin, so he prescribes thyroid. This treatment is of no more value, and the patient gradually drifts out of medical care again. At this stage she may develop delusions and be transferred to a psychiatric hospital, where the interests of the staff are naturally focused rather more on the mental than the physical aspects.

C. After a few years the patient has some minor illness and, within a day or two, lapses into coma. It is now obvious that she is seriously ill and not just an idle slattern, and she is admitted as an emergency case to the hospital. If and when the coma has been successfully treated, the question of whether her hypopituitarism will be recognized depends on whether the hospital staff are aware of the true syndrome. They will not arrive at a correct diagnosis if they have the common misconception that patients with severe hypopituitarism have cachexia and progeria. In such a hospital, the condition continues

to be regarded as a rarity. On the other hand, in hospitals where one or two of these cases have been diagnosed correctly and then studied, nearly all subsequent cases are identified without difficulty, and the frequency of the condition is found to be much higher than had been supposed.

No reliable estimate can be given of the proportion of cases which are missed. Nevertheless, almost every patient personally studied had been under medical care at home or in hospitals on and off for several years before the real diagnosis was even considered. The number of cases that are continuing in an undiagnosed state is certainly relatively high.

### Cases Recorded in the Literature

A study of the literature supports the view that the common belief in the rarity of the disease arises from the fact that the diagnosis is often missed. Now that the condition is becoming better recognized, the number of cases reported in the literature is increasing rapidly. What is more significant is that, whereas single cases used to be recorded because of their rarity interest, a number of individual authors during the last few years have identified several cases each, and have published them as series. Table III shows the number of cases recorded in the last 45 years.

TABLE III. NUMBER OF CASES OF SEVERE POSTPARTUM HYPOPITUITARISM REPORTED IN THE LITERATURE

PERIOD	WITH AUTOPSY	CLINICAL RECORD ONLY
1908 to 1939	33	32
1939 to 1949	35	69
1949 to 1953	29 (including present series)	125

Most of the references to cases published before 1949 have been collected in previous reviews (Sheehan, 1939; Sheehan and Summers, 1949). The bibliography of the present paper contains references to the cases published since 1949 and also to a few others omitted from the earlier reviews. These are arranged in three lists. The very great majority of the cases in the first two lists appear to have been of severe grade, but there is insufficient information to decide on the severity of the cases in the third list.

### Present Cases

The number of cases diagnosed clinically in this district in the last few years is relatively large; in several of the local hospitals it is considered that postpartum hypopituitarism is rather commoner than myxedema and much more common than Addison's disease. As far as can be judged, the criteria required for clinical diagnosis are just as strict here as elsewhere. Nevertheless, in order to avoid possible errors, it appears advisable to restrict the present consideration to cases in which the clinical diagnosis has been proved by autopsy. Even with this limitation, difficulties can arise.

The number of cases that come to autopsy in this district is not inconsiderable, though admittedly care is taken to ensure as far as possible that the

cases which have been diagnosed clinically are examined after death. In earlier papers accounts have been given of 6 autopsied cases of severe prolonged hypopituitarism due to postpartum necrosis, and also of 7 cases where the scars of smaller necroses of this type were found at autopsy. To this series may be added the following 7 cases examined clinically and at autopsy here during the four-year period, 1950 to 1953, and 2 other cases in which the organs were received from pathologists elsewhere for examination: Case 2 from Dr. Griffiths of Birmingham, and Case 4 from Dr. Parry of Llandough. Thanks are also due to both these pathologists for the clinical records of the two cases.

CASE 1.—PM., para iii, aged 41 years at death.

*Clinical Course.*—

The first two pregnancies ended in miscarriage. The last pregnancy occurred when she was 31. Numerous very large fibroids were present, and one of these occupied much of the pelvis. She was delivered at term by cesarean section, and very severe hemorrhage occurred from large veins over the uterus. No further obstetric details are now available, but there was no lactation in the puerperium. Subsequently she had permanent amenorrhea, great sensitivity to cold, physical weakness and extreme sloth, so that she neglected her home and family and appeared quite indifferent to her surroundings. Her pubic and axillary hair disappeared and the eyebrows became scanty. The hair on her head became somewhat thin but retained its color. The skin was dry and pale and the nipple areolae were depigmented. She gained steadily in weight in the course of the next few years, and developed a puffy face suggestive of hypothyroidism or renal edema.

The first detailed examination was made when she was 37. The vulva and vagina were atrophic, the cervix only a dimple, and the uterus scarcely palpable. The thyroid gland could not be felt. The blood pressure was 120/80 and electrocardiograms showed a prolonged P-R interval. Gross pyuria was present. An insulin tolerance test using 1.5 units intravenously gave the following figures.

MINUTES	0	20	30	45	60	90	120
Blood sugar	79	59	44	39	45	45	47
(mg. per 100 c.c.)							

There were no detectable 17-ketosteroids in the urine. Kepler tests showed poor diuresis and an index of 11. Blood examinations gave mean figures for red corpuscles of 3.2 million per cubic millimeter and for hemoglobin of 72 per cent. Blood chemistry showed urea 42 mg., sodium 300 mg., potassium 18 mg., and chlorides (as NaCl) 590 mg. per 100 c.c.

She was treated with testosterone and thyroid with only moderate benefit. Later she was given cortisone in doses of 100 mg. daily; this produced a dramatic increase of her physical and mental energy but after 12 days she developed psychological changes and refused further treatment. The details are recorded by Summers and Sheehan, 1951. During the last few years of her life she had several episodes of coma. The last two of these attacks were identified as hypothermic and were cured by warm baths (Sheehan and Summers, 1952).

Several months later she went to bed apparently in her usual state of health, and was found dead next morning.

*Autopsy Findings.*—

The body was of good nutrition with a weight of 152 pounds for a height of 65½ inches.

The pituitary had a normal stalk and pars tuberalis but the posterior lobe showed areas of atrophy. The anterior lobe was represented by a little fibrous tissue in which only a tiny lamina of parenchymal cells could be found, estimated as about 1 per cent of the original gland. The thyroid was red and weighed 9.4 grams (normal, 20 to 30 grams). Microscopically about one-third consisted of small acini with flat epithelium and normal

colloid content; the remainder was fibrous tissue with a heavy lymphocytic infiltration, often concentrated into follicles without germinal centers. The adrenals were very small with a combined weight of 1.2 grams (normal, 10 to 15 grams). The cortex was almost entirely replaced by hyaline fibrous tissue, but there were a few areas of parenchyma varying in depth from 0.1 to 0.2 mm. (normal, 1 to 1.5 mm.). The medulla was very atrophied. The ovaries weighed 3.0 grams together (normal 7 to 15 grams), and were flat and smooth. They contained a fairly large number of primordial follicles and several old corpora albicantia, but no intermediate stages. The uterus contained eight shrunken fibroids varying from about 0.5 to 1.5 cm. in diameter. The total weight was 80 grams. Microscopically the myometrium consisted of little else but hyalinized blood vessels and the endometrium was represented only by occasional tiny glandular structures. The fibroids were necrosed and calcified. The parathyroids were rather large and contained several large islets of eosinophil cells. The thymus consisted only of a few flat laminae of epithelial cells in the anterior mediastinal fat, and had no Hassall corpuscles or lymphocytes. The pancreas showed numerous islets of Langerhans of about normal size.

The breasts were normal to the naked eye; microscopically there were a number of atrophic acini in the fibrous tissue. The lymph nodes had a normal structure apart from having no recognizable germinal centers in the follicles. There was no significant splanch-nomieria; the heart weighed 275 grams (normal 260 to 340 grams), the liver 1,250 grams (normal 1,400 to 1,800 grams) and the kidneys 190 grams together (normal 260 to 340 grams). These weights are however rather small in view of the body weight. The other pathological findings were bilateral bronchopneumonia, minor scarring of one angle of the mitral valve, about 50 minute black gallstones, healed pyelonephritis of the right kidney, and severe chronic cystitis.

*Comment.*—

This was a typical case of gross postpartum necrosis. Clinically the patient was of very hypothyroid type and might well have been described as having "pituitary myxedema." The thyroid was certainly very small but the most striking secondary change found at autopsy was the very severe atrophy of the adrenals. Usually in cases of hypopituitarism the adrenal medulla is only slightly smaller than normal, and thus looks relatively large by comparison with the shrunken cortex. In the present case both cortex and medulla were involved equally.

The persistence of primordial ova in the ovaries of these patients up to the age of the normal menopause has been discussed elsewhere (Sheehan, 1953).

CASE 2.—CH., para vii, aged 57 years at death.

*Clinical Course.*—

The last pregnancy occurred when she was 38. She had a severe antepartum hemorrhage at 8 months' gestation, and was delivered the day afterward. She received several blood transfusions and was not expected to survive.

Since that time she had permanent amenorrhea and became apathetic and was extremely sensitive to cold. For many years she had no medical care, and finally died in coma.

*Autopsy Findings.*—

The body was well nourished. The skin was very white; much erythema ab igne was present over the shins. There was no pubic or axillary hair, the eyebrows were thin, and the scalp hair dark and plentiful.

The pituitary consisted of a normal stalk, pars tuberalis, and posterior lobe; the anterior lobe was represented by a small mass of fibrous tissue in which microscopic examination did not reveal any remaining parenchyma. The thyroid was small (12.5 grams). Histologically the acini were small and contained little or no colloid, and their epithelium had an unusual foamy appearance. The gland was subdivided by many thick septa of fibrous tissue. The adrenals were so small that they were found only after very prolonged search. Their combined weight was 0.4 gram. Histologically they consisted of



a fibrous capsule 0.15 mm. thick, a very atrophic cortex also 0.15 mm. deep, and an equally atrophic medulla containing few cells. There was no fibrous band between cortex and medulla. The ovaries were small (combined weight 3.0 grams) and showed no ova; one large corpus albicans was seen. The uterus weighed 40 grams. Its myometrium was represented only by hyalinized remains of arteries; the endometrium was very thin and showed a few atrophic glands.

The heart was very small (155 grams), but the liver (1,310 grams) and the kidneys (215 grams together) were only moderately atrophied.

*Comment.—*

The clinical history is scanty as it was obtained only from relatives after the patient's death. Nevertheless, it is quite clear from the clinical and the pathological accounts that she had postpartum necrosis of the whole anterior lobe, giving a severe hypopituitarism subsequently.

The atrophy of the adrenals was even more marked than in Case 1, and was as severe as is seen in many cases of Addison's disease. Such extreme atrophy is unusual in hypopituitarism. Both these patients had the typical complete absence of skin pigmentation. It is thus clear that the pigmentation of Addison's disease depends not only on the absence of adrenal function but also on the presence of an active anterior pituitary.

CASE 3.—BL., para iii, aged 45 years at death.

*Clinical Course.—*

At the age of 36 the patient suffered a postpartum necrosis and had typical severe hypopituitarism subsequently. The clinical course of this patient has been recorded previously as Case 6 by Cooke and Sheehan (1950). Only a few biochemical details need be added to that description. There was no detectable urinary excretion of 17-ketosteroids. An insulin tolerance test, using 1.5 units intravenously, gave the following blood sugar levels: 62 at 0 minutes, 42 at 30 minutes, 42 at 60 minutes, and 54 at 120 minutes. Blood chemistry showed sodium 300 mg., potassium 20 mg., chlorides 520 mg., and cholesterol 220 mg. per 100 c.c. Hematology showed a red blood count of 3.8 million with hemoglobin 82 per cent.

She was treated first by implantation of portions of a virilizing adrenal adenoma removed from a young girl (Jeffcoate, 1948). The graft seemed to have some activity for 3 months but subsequently lost its effect. After this she was given androgen treatment: originally by subcutaneous injection of 100 mg. testosterone propionate each week and later by sublingual administration of 20 to 30 mg. of methyl testosterone daily. This treatment was continued for 4 years and kept her in fairly good health so that she was able to do her housework. It produced a thin growth of rather straight hair over the mons, a slighter growth of hair in the axillae, and a slight growth of beard and moustache, but no thickening of the scanty eyebrows. The scalp hair remained as it had been previously: of soft texture but of normal color and amount. There was no increase of skin pigmentation.

At the age of 45 she noticed a small mass in the upper outer quadrant of the left breast. A biopsy specimen was removed under gas-oxygen anesthesia. She recovered consciousness an hour after the operation but became comatose soon after. Intravenous glucose was given but she remained comatose and died 18 hours later.

*Autopsy Findings.—*

The body appeared well nourished and had plenty of subcutaneous fat.

The anterior lobe of the pituitary was replaced by a small mass of connective tissue. Histological examination showed only a few tiny islets of foamy chromophobe cells representing about 2 per cent of the original parenchyma. The thyroid was not much reduced in size (weight 17.0 grams). Histologically its acini were rather small but were full of colloid, and their epithelial lining was very flat. There were numerous fibrous septa but only moderate lymphocytic infiltration. The adrenals were small (combined weight 3.8 grams); on microscopic examination the capsule was thick, the cortex was very

thin (0.2 to 0.3 mm.), and the corticomedullary junction fibrosed. The medulla appeared normal. The ovaries were very small (combined weight about 3 grams); they contained numerous primordial ova with dense cytoplasm, and several corpora albicantia but no developing follicles. The uterus was small (about 50 grams) and had a very atrophic endometrium. The pancreas showed only normal numbers of islets and these were not enlarged.

There was well-marked splachnomicria: the heart weighed 175 grams, the liver 690 grams, the kidneys together 135 grams. The lymph nodes had no germinal centers in the follicles. The site of the adrenal tumor graft showed only scar tissue on microscopic examination. The tumor in the left breast was a scirrhous carcinoma about 2 cm. in diameter; its histological appearances were in no way different from those seen in patients with normal pituitaries. There was very early bronchopneumonia in the lower lobe of the right lung.

*Comment.—*

This case is of particular interest at the present time. Several recent accounts of experimental studies have suggested that the pituitary plays an important role in carcinogenesis; growth hormone was found to stimulate the development of carcinoma in mice and hypophysectomy to retard it. However, in human beings there is no evidence that hypopituitarism prevents the occurrence of carcinoma. In a review of the literature, Archer (1953) tabulated 9 patients with severe or moderate hypopituitarism and 4 patients with mild hypopituitarism who had developed carcinoma in various organs. To that list may be added the case of McKay, Burnett, and Burrows (1950) in which carcinoma of the gall bladder occurred in a patient suffering from hypopituitarism; she had an "empty sella" with loss of three-fourths of the anterior lobe. The distribution of the various carcinomas reported is stomach, 4 cases; bronchus, 3 cases; cervix, 2 cases; and esophagus, colon, gall bladder, mediastinum, and thyroid, 1 case each. Archer pointed out that up to 1953 there had been no published case of carcinoma of the breast or ovary in patients with hypopituitarism, and speculated very tentatively regarding the possible advantages of surgical subtotal hypophysectomy as a therapeutic measure for malignancy of the breast. As against this, there must be set the present case of carcinoma of the breast, which developed in a patient who had already been suffering for 9 years from almost total hypopituitarism. This single case raises serious doubts about the theoretical basis of hypophysectomy in the therapy of carcinoma of the breast.

There have, however, been a number of attempts to treat this and other kinds of malignant tumors by hypophysectomy. A case of carcinoma of the breast treated by hypophysectomy was reported by Perrault (1952); further details are given by Perrault and associates (1952) and by Le Beau and Perrault (1953). These latter authors mention that they have since performed hypophysectomy for a number of other cases of carcinoma of the breast, and also of the testis and the uterus. Shimkin and co-workers (1952) did therapeutic hypophysectomy for a malignant melanoma. Luft and Olivecrona (1953) report 9 hypophysectomies for carcinoma of the breast and 3 for other carcinomas; they review most of the literature on this subject. There is a brief reference by Hart (1953) to cases of adrenal carcinoma treated by hypophysectomy in America. As yet it is too early to assess the practical results of this method of treating carcinoma, and judgment must therefore be suspended.

CASE 4.—UP., para i, aged 36 years at death.

*Clinical Course.—*

Her only pregnancy occurred when the patient was aged 30. She had a difficult breech delivery with complete perineal tear. No other obstetric details are available. On the third day of the puerperium she developed pyrexia, severe headache, dimness of vision, and swelling of one leg. She was admitted to the hospital and, after treatment with penicillin, she recovered in about two weeks. There was no lactation.

Six months later she was admitted to the hospital for perineal repair. She had failed to recover her strength, her blood pressure was 90/60 and her weight had fallen from her normal 102 pounds to about 90 pounds. There had been no menstruation. At the

operation it was noted that the vagina and vulva were extremely atrophic; the pubic and axillary hair were still present. Soon after this she had two menstrual periods, each lasting for one day. Subsequently there was permanent amenorrhea.

Eighteen months after the delivery she had abdominal pain and vomiting and diarrhea for two weeks and then within a few hours gradually became comatose. Her temperature was 102° F. There was neck rigidity but the cerebrospinal fluid showed no abnormality apart from a glucose content of only 34 mg. per 100 c.c. She recovered quickly after the intravenous administration of 2 L. of 20 per cent glucose solution. On more detailed examination a few days later, it was noted that there was no pubic or axillary hair and that the eyebrows were very thin. The skin was very pale and smooth. Cerebration was retarded, speech was slow, and there was little physical activity. The blood pressure varied from 95/65 to 110/80. The urinary excretion of 17-ketosteroids was 0.05 mg. per day. Kepler's test gave an index of 17. Electrocardiograms showed low voltages and absence of T waves in Leads II and III. The blood cholesterol was 335 mg. per 100 c.c. The fasting blood sugar ranged between 71 and 87 mg. per 100 c.c. The hemoglobin was 75 per cent.

At 2 years after the delivery she appeared rather better, with blood pressure 110/80, hemoglobin 96 per cent, and weight 97 pounds. Three years after the delivery, symptoms of cystitis were rapidly followed by another episode of coma. The blood pressure during the coma was 95/50. She recovered after intravenous glucose. Subsequently she was treated with testosterone and thyroid.

Six years after the delivery she was again admitted to the hospital in deep coma. The pulse was rapid but too weak for blood pressure estimation. The pupils were pin point; there was no rigidity of the neck. Her temperature was 98° F. on admission but gradually rose to 102° F. Some pubic hair was now present, as a result of the testosterone therapy. The coma was treated with intravenous glucose, ACTH, DOCA, and adrenal cortical extract but these had no effect and she died within 24 hours.

#### *Autopsy Findings.—*

The body was of good nutrition.

Almost the entire anterior lobe of the pituitary was replaced by a small mass of fibrous tissue in which there were very tiny remnants of parenchyma representing less than 1 per cent of the original lobe. These were very vacuolated cells, presumably chromophobes. The posterior lobe had a light infiltration with atrophic basophil cells. The stalk appeared normal and had a thin pars tuberalis. The thyroid was atrophied (5.5 grams). Its acini were very small; they had low cuboidal epithelium and contained colloid. They were subdivided into lobules by broad fibrous septa. A few foci of lymphocytic infiltration were present. The adrenals were small, with a combined weight of 5.5 grams. The cortex was very atrophied, varying from 0.1 to 0.35 mm. in thickness. The medulla appeared normal. The pancreas had very numerous islets which appeared to be proliferating. The parathyroids were of full normal size. Histologically they contained only chief cells with no eosinophil cells. The ovaries together weighed 4.0 grams. They contained numerous primordial ova and a number of old corpora albicantia, but there were no developing follicles or corpora lutea. The uterus was very small, weighing only 26 grams. Its myometrium had great atrophy of muscle fibers, leaving most of the nuclei intact. The endometrium was very atrophied and rarely reached 0.2 mm. in thickness.

There was atrophy of the heart (170 grams), of the kidneys (combined weight 200 grams), and to a less extent of the liver (1,260 grams). The brain was rather edematous.

#### *Comment.—*

It is of interest that this patient had two slight menstrual periods several months after the delivery; this is presumably to be related to the activity of the tiny remnants of anterior lobe parenchyma. Otherwise the clinical course and the manner of death were very typical. Even the gaps in the record are characteristic.

CASE 5.—RO., para v, aged 58 years at death.

*Clinical Course.*—

The patient was 29 at the time of the last pregnancy which ended with a miscarriage. No other information is available about the delivery or the puerperium.

Her memory during her last six months was very bad, and she could give no account of her health since the delivery. Her first medical records begin when she was 33; at that time she was suffering from amenorrhea, physical weakness, sensitivity to cold, absence of sweating, lack of appetite and of thirst, anemia, and occasional dysuria. When she was 40 the left breast was removed, but the reason for this is unknown. Six months before her death her condition began to deteriorate, and she had occasional attacks of vomiting. It was then noted that she had no axillary and practically no pubic hair, though some hair was present over the labia. The hair of the head was normal. Her face was very pale and waxy but there was some yellowish pigmentation over the forehead and forearms. The remaining nipple areola was depigmented but there was some brownish erythema ab igne over the shins. Her weight was 104 pounds. The blood pressure was 70/40. The blood count showed red blood cells 3.2 million per cubic millimeter and hemoglobin 58 per cent. The blood urea was 33 mg. and the serum sodium 312 mg. per 100 c.c.

She was admitted to the hospital 6 weeks before death. She had some cough but no sputum. X-ray examination showed bilateral pulmonary tuberculosis. Her weight had fallen to 86 pounds and the blood count to red blood cells 2.4 million per cubic millimeter and hemoglobin 36 per cent. The bone marrow showed normoblastic erythropoiesis. The blood reticulocytes were 3.8 per cent. A histamine test meal showed free acid. The Kepler test gave a maximum diuresis of 37 c.c. per hour, and the index was 9.5. Serum sodium was 290 mg., potassium 22 mg., urea 38 mg., and glucose 62 mg. per 100 c.c. The urine output was about 600 to 800 c.c. per day. The blood pressure varied in the range of 90/50 to 100/55. There was no pyrexia.

While in the hospital she was given blood transfusions and intravenous iron in view of the anemia. One attack of semicoma was treated successfully with intravenous glucose. Five days later she collapsed and died. A blood sample taken at about the time of death contained glucose 55 mg., urea 47 mg., sodium 350 mg., and potassium 27 mg. per 100 c.c.

*Autopsy Findings.*—

The body was slender but not emaciated.

To the naked eye, the anterior lobe of the pituitary was represented by a thin layer of fibrous tissue in the floor of the sella. Microscopic examination showed very occasional islets of parenchyma (mainly basophil cells) in this fibrous tissue, estimated as perhaps 2 per cent of the original lobe. The posterior lobe and the stalk were normal. The thyroid was extremely small (2.4 grams). It consisted almost entirely of fibrous tissue in which there were occasional tiny islets of parenchyma. These acini were very small. They were lined by rather cuboidal eosinophil epithelium and were full of colloid. There was no lymphocytic infiltration. The adrenals were very small (combined weight 2.4 grams). Histologically the cortex was very atrophic and had an average thickness of 0.2 mm. Its cells contained little lipid. The medulla was not as prominent as usual. The parathyroids appeared normal. They contained several patches of eosinophil cells. The ovaries (2.2 grams together) contained no primordial ova but there were several corpora albicantia. The uterus (59 grams) had a fibrosed myometrium, but its endometrium was almost 1 mm. in thickness.

There was definite splanchnomicria: the heart weighed 170 grams, the liver 800 grams, the kidneys combined 120 grams. The lungs showed extensive tuberculosis with consolidation of the right middle lobe by firm tuberculous bronchopneumonia, nodular lesions and a cavity in the left upper lobe, and multiple small tubercles in the left lower lobe. There was much pleural effusion on the left side. There was some scarring of old pyelonephritis in the right kidney, and the bladder showed slight cystitis cystica. One pigment gallstone was present.



*Comment.—*

This patient had a severe hypopituitarism which appears to have probably been due to a postpartum necrosis, though an exact history is lacking. In this case the atrophy of the thyroid was a prominent pathological feature though it had not given any clinical impression of "pituitary myxedema." As an example of the standard problems of diagnosis, it may be mentioned that the correct diagnosis was made clinically at her final admission, but that at various times before this she had been considered to be suffering from hypochromic anemia, pernicious anemia, hypothyroidism, Addison's disease, avitaminosis, and occult gastric carcinoma. The appropriate treatments for all except the last of these conditions had been given, but without benefit.

In view of the carcinoma of the breast in Case 3 it is unfortunate that no information can be obtained as to the reason for the mastectomy in the present case. The pulmonary tuberculosis, though extensive, was remarkably symptomless, as sometimes happens in these cases.

CASE 6.—PI., para iv, aged 50 years at death.

*Clinical Course.—*

The earlier history was elicited with great difficulty during the patient's final stay in the hospital. At that time she alternated between stupor and a querulous mental confusion; her memory was very poor and she gave inconsistent and often contradictory accounts, varying from one day to the next.

The only definite fact was that her last pregnancy occurred when she was 28, and that she had severe toxemia and was in convulsions at the time of delivery. She was kept in the hospital for three months afterward. She said that from that time she was always very pale, and that the pubic hair which had been shaved never grew again. She also said that menstruation continued regularly until she was 40, but this statement may be doubted. After the age of 40 she suffered from chronic bronchitis, weakness, and a tendency to fainting. Her weight, which had previously been 104 pounds, with a height of 60½ inches, gradually fell to about 90 pounds. When she was 47 there was a period of severe mental disturbance. At that time she was very pale but had a normal blood count.

During the last year of life her general health deteriorated though her weight remained constant. During the last three months she had several attacks of coma lasting a day or two. These attacks were preceded by drowsiness. During them she was very cold and pulseless, with a heart rate varying between 70 and 160. In the intervals her blood pressure ranged between 75/50 and 120/70. Blood counts gave mean figures of red blood cells 4.0 million and hemoglobin 79 per cent, with eosinophils 10 per cent. Blood chemistry showed cholesterol 150 mg., sodium 320 mg., potassium 18 to 21 mg., and glucose 120 mg. per 100 c.c. There was no axillary or pubic hair, but the eyebrows and hair of the head were normal. The thyroid was not palpable.

During the last three weeks there was much vomiting and she became pyrexial. She sank slowly into a permanently comatose condition before death.

*Autopsy Findings.—*

The body was thin.

The anterior lobe of the pituitary was almost replaced by a flat layer of fibrous tissue on the floor of the sella. A very thin remnant of parenchyma was found microscopically in this tissue; it represented about 2 per cent of the original lobe, and consisted of basophils and vacuolated chromophobe cells. The posterior lobe was slightly fibrosed. The stalk appeared normal and had a very thin pars tuberalis. The thyroid was small (5.4 grams) and consisted of very small acini filled with pale-staining colloid and lined by a low cuboidal epithelium. The gland was divided into lobules by fibrous septa which had very little lymphoid infiltration. The adrenals (combined weight 4.8 grams) were moderately atrophied. The cortex was usually 0.3 mm. deep but in a few places reached 0.5 mm. The fibrous capsule was not significantly thickened. The medulla appeared normal. The pancreas (48 grams) contained very large numbers of islets, some of which were unusually big. The ovaries (combined weight 2.7 grams) were flat. Two primordial follicles

were found, one of which had a double layer of cells around the ovum. There were several corpora albicantia. The uterus (55 grams) had an endometrium 0.6 mm. deep which contained atrophic glands which were somewhat cystic. The inner third of the myometrium had a relative excess of nuclei due to loss of cytoplasm from muscle cells; the outer two-thirds consisted only of coiled hyaline blood vessels.

The heart (185 grams) and liver (850 grams) were small, but the kidneys (210 grams) were less atrophied. There was some emphysema of the lungs with a terminal bronchopneumonia.

*Comment.—*

This was a case of severe hypopituitarism probably due to a postpartum necrosis. The clinical history is not clear or reliable enough to establish this etiology; in particular it is difficult to reconcile the menstrual history with the failure of pubic hair to grow after the delivery. The appearance of the pituitary at autopsy was quite typical of a healed necrosis.

CASE 7.—DO., para xiii, aged 61 years at death.

*Clinical Course.—*

Her last delivery occurred when the patient was aged 36. There was severe antepartum and postpartum hemorrhage; further obstetric details are not now available. Since that time she had permanent amenorrhea. She never recovered her normal health and was always feeble and very sensitive to cold.

When she was 46 she developed pulmonary tuberculosis of both apices, with positive sputum and occasional slight hemoptysis. This gradually became quiescent during the next ten years.

At the age of 60 her appetite became very poor and she complained of weakness of the legs and numbness of the hands. Six months later she became mildly demented for a few days and was admitted to the hospital. The face was pale and the nipple areolae depigmented. The hair of the head was normal in color and texture, but the eyebrows were sparse, and there was no axillary or pubic hair. The thyroid could be palpated without difficulty. Her speech was slow and the hand-grip weak. Her height was 59 inches and her weight 85 pounds, but this increased to 96 pounds during her 8 weeks' stay in the hospital. The blood pressure ranged between 130/75 and 140/90, and the pulse rate was usually about 80. Electrocardiograms showed a left axis deviation but no other abnormality. Blood counts gave mean figures as follows: Hemoglobin 63 per cent; red blood cells 3.7 million per cubic millimeter; white blood cells 5.0 thousand per cubic millimeter. The bone marrow showed normoblastic erythropoiesis. A test meal showed no free acid. The basal metabolic rate was -26 and -32, and the blood cholesterol 195 mg. per 100 c.c. The urinary excretion of 17-ketosteroids ranged between 0.27 and 0.53 mg. daily. On a Kepler diuresis test the maximum output of urine was 70 c.c. per hour. Two insulin tolerance tests were carried out, using 0.03 unit per kilogram of body weight intravenously. The results were as follows.

MINUTES	0	20	40	60	90	120
Blood sugar (mg. per 100 c.c.)	53	26	28	28	28	30
	55	30	29	25	35	35

She was given weekly injections of 100 mg. testosterone propionate for the last month of this stay in the hospital but abandoned treatment soon after discharge.

After a further 6 months she became mentally deranged again and was readmitted to the hospital for a few days. The blood pressure was 180/110, fasting blood sugar 70 mg., serum sodium 300 mg., chloride (as NaCl) 503 mg., and urea 29 mg. per 100 c.c. The Kepler test gave a maximum hourly excretion of 67 c.c. and an index of 22. The blood count was unchanged. She was given testosterone treatment for 3 weeks but again defaulted.

Six months later she returned for treatment and was given testosterone again for 4 weeks. At this stage her weight had increased to 110 pounds but the anemia was rather worse: hemoglobin 56 per cent; red blood cells 3.1 million per cubic millimeter; white blood cells 5.5 thousand per cubic millimeter. Some puffiness was present across the root of the nose and around the eyes, so that she looked rather myxedematous. There was no regrowth of body hair or increase of the skin pigmentation.

On the day after the fourth weekly injection of testosterone she became drowsy and uncooperative. The next day she had three epileptiform convulsions and lapsed into unconsciousness. She was very restless and tossing about, so 5 c.c. of paraldehyde was injected subcutaneously. Following this she was deeply comatose and quiet. About 24 hours later she became severely collapsed and apparently moribund, with very cold face and extremities and no pulse. The rectal temperature was 97° F. and the heart rate 90 by auscultation. There was some loose melena. Intravenous glucose and cortisone produced no recognizable effect. She remained in this condition for 36 hours before death.

*Autopsy Findings.—*

The body was of good nutrition.

The pituitary showed replacement of nearly all the anterior lobe by a small mass of pale brown connective tissue. Microscopically there were thin laminae of parenchyma remaining at the upper and lower surfaces. These represented less than 10 per cent of the original gland, and consisted mainly of vacuolated chromophobe cells with occasional basophils and scanty poorly-stained eosinophils. The stalk and posterior lobe were normal. The thyroid was very atrophied and dull red-brown in color. Each lateral lobe contained an old fibrosed adenoma, which on one side was calcified. The whole gland including these adenomas weighed 15.3 grams. Microscopically the acini were small and lined by flat epithelium. All contained colloid. They were divided into lobules by coarse fibrous septa in which there were many patches of lymphocytes. The adrenals were small (weight 5.7 grams together). The cortex was very thin (0.2 to 0.3 mm.) and contained lipoid. There was no pigmentation of its deeper portion. The medulla was of full normal amount and made up most of the substance of the gland. The capsule was not thickened. The ovaries and uterus were small, but not remarkably so in view of the age of the patient. Several old corpora albicantia were present. The pancreas contained very many large islets of Langerhans.

The heart was large (355 grams) and its left ventricle was rather thick. The liver (960 grams) and the kidneys (210 grams together) were small. The lymph nodes had no germinal centers in the follicles. There was an old softening, 1 cm. in diameter, in the white matter of the left frontal lobe just in front of the caudate nucleus. Both lungs showed old fibroid tuberculosis of the upper lobes, without gross evidence of recent activity. The duodenum and upper jejunum were greatly dilated and congested, and their peritoneal surfaces were matted together by fresh fibrinous adhesions. The related mesentery was very edematous. The gall bladder contained one soft pigment stone.

*Comment.—*

This was a clear case of postpartum necrosis and clinically appeared severe. The thyroid and adrenal cortex showed the characteristic atrophy. Nevertheless, the damage to the pituitary was not quite as complete as in the preceding cases.

There was sometimes hypertension, which may account for the hypertrophy of the left ventricle. This is not a common complication of hypopituitarism but it has been observed in a certain number of proved cases, and thus cannot be considered as evidence against the diagnosis.

CASE 8.—CL., para i, aged 62 years at death.

*Clinical Course.—*

Her only delivery occurred when the patient was 26. There was severe hemorrhage due to a retained placenta which had to be removed manually. She became unconscious as a result of the blood loss. The breasts did not become engorged, and there was no lactation. Subsequently there was amenorrhea, apart from one week of uterine bleeding when

she was 34. The pubic and axillary hair disappeared gradually but completely, though some hair remained on the labia. The eyebrows were unaffected and the head hair retained its normal consistency and its dark brown color until death. The skin was soft and rather pale but there was the unusual finding that the nipple areolae retained their pigment and that there was brown erythema ab igne over the shins. The thyroid was easily palpable. She was very sensitive to cold and was always weak and tired so that she neglected her home. Nevertheless, she could get about and do a little housework, she retained her interests and read books, and she replied to questions quickly and clearly with a voice of good strength.

Various investigations were made when she was 58 and 59. The daily excretion of 17-ketosteroids was 2.6 and 2.8 mg. The mean urinary output was 860 c.c. per day. The blood cholesterol was 250 mg. per 100 c.c. Blood counts gave red blood cells 4.1 to 4.6 million per cubic millimeter with hemoglobin 85 to 90 per cent. The fasting blood sugar was 100 mg. per 100 c.c. Her blood pressure fluctuated widely; it was 80/50 on one occasion and 220/110 on another. Electrocardiograms showed no abnormality.

This clinical picture of an incomplete hypopituitarism was complicated by a second chronic illness. When she was 51 she had an acute lung infection. For the remainder of her life she had chronic cough and copious sputum, and there were pyrexial attacks lasting a week or two every few months. When she was 58 radiological examination showed bronchiectasis of both lungs and there was a constant polymorphonuclear leukocytosis of 12 to 18 thousand. During this period her appetite was always poor so that her nutritional state deteriorated severely; at the age of 58 her weight was only 63 pounds though a year later it had improved to 71 pounds.

After the age of 61 she became gradually more feeble. She was kept in the hospital during the last month but did not respond to testosterone therapy, and became progressively weaker until death.

#### *Autopsy Findings.—*

The body was very emaciated.

The pituitary showed a normal stalk and posterior lobe, but the anterior lobe was represented only by a thin lamina of parenchyma lining the floor of the sella. This consisted mainly of eosinophil cells and of foamy chromophobe cells, and was estimated to be about 10 or 15 per cent of the original gland. The thyroid (28 grams) was of normal size and had a diffuse colloid appearance to the naked eye. Histologically the acini were of various sizes from small to full normal, and contained plenty of colloid. There was no fibrosis and no lymphocytic infiltration. The adrenals (combined weight 5.2 grams) were a little smaller than normal. They had a relatively large medulla. The cortex was about 0.7 mm. in thickness and was full of lipoid; it showed no pigmentation in its deeper layers. The parathyroids were slightly smaller than usual. The pancreas contained an abnormally large number of islets which were of ordinary size. The ovaries showed no primordial ova on histological examination; several rather large corpora albicantia were present. The uterus was of ordinary postmenopausal size.

The heart (280 grams) was not atrophied. There was no atheroma of the coronary arteries or aorta. The liver was small; its left lobe was replaced by a very old hydatid cyst weighing 100 grams and the remainder of the liver weighed 760 grams. The kidneys were also small (combined weight 150 grams). There was extensive bronchiectasis involving the lower lobes of both lungs and the right middle lobe, with gross fibrosis of these lobes and adhesions of cartilaginous consistency over them. All the bones showed severe senile osteoporosis.

#### *Comment.—*

This patient had a subtotal postpartum necrosis. She did not develop the full clinical picture of a very severe hypopituitarism, and the autopsy findings confirmed that the endocrine disturbance was only a partial one. The emaciation developed during the last ten years and was the result of the severe bronchiectasis. The remaining anterior lobe



parenchyma was sufficient to allow the patient to remain alive until she became emaciated; a patient with severe hypopituitarism would probably have died soon after the onset of the loss of weight.

Patients with hypopituitarism who develop pneumonia are liable to develop necrosis of part of the lung. This can remain as a slough in an abscess cavity with remarkably few symptoms for several months. Some such process may have been the cause of the bronchiectasis in the present case.

CASE 9.—TU., para v, aged 57 years at death.

*Clinical Course.*—

At her second delivery when she was 26 this patient had very severe hemorrhage in the third stage and became unconscious. She did not lactate. Menstruation began again a few months later and continued regularly apart from normal pregnancies when she was 29, 30, and 32. There was some illness of indefinite character (attacks of fainting and nervousness) when she was 34. After this she had permanent amenorrhea. At the age of 49 there was a short febrile illness of influenza type. She never recovered her strength and was unable to do any housework subsequently. The pubic and axillary hair disappeared at about this time, and the eyebrows became very thin. The hair of the head remained dark brown and of normal amount. Her weight was unchanged at 120 pounds. During the next 5 years she had much bronchitis and three attacks of pneumonia.

About 6 months before death she began to have anginal attacks and lost her appetite. Her general condition deteriorated and she gradually lost weight, so that she weighed only 100 pounds a week before death. On admission she was very pale, and had no pigmentation of the nipple areolae. There was no sweating or axillary secretion. The genital tract was superinvolved. The thyroid could not be palpated. The blood pressure varied from 120/70 to 140/85. Electrocardiograms showed no abnormality, with normal voltages and no disturbance of T waves. The urinary excretion of 17-ketosteroids was 0.7 mg. per day. A diuresis test was made, using 1,600 c.c. of water and recording the hourly output of urine for 14 hours. The first three hourly specimens were of 25 c.c. each, and the subsequent ones varied between 12 and 21 c.c.; any diuresis was certainly delayed over 14 hours. An insulin tolerance test, using 1.5 units of insulin intravenously, gave the following figures.

MINUTES	0	20	40	60	120
Blood sugar	49	29	29	23	23
(mg. per 100 c.c.)					

At the end of the test she was semicomatose, but recovered after the administration of intravenous glucose. Other biochemical studies of the blood showed cholesterol 119 mg., potassium 28 mg., and phosphate 3.5 mg. per 100 c.c.

After she had been in the hospital for three weeks she lapsed into hypothermic coma but recovered after the application of warmth. A week later a similar attack of coma occurred with a temperature again below the scale of the clinical thermometer, and a very slow heartbeat with impalpable pulse. The muscles were spastic and the reflexes normal and brisk. She was given intravenous glucose, but died soon after.

*Autopsy Findings.*—

The body was of normal nutrition, the subcutaneous fat over the sternum being nearly 2 cm. deep.

The pituitary showed no abnormality of the stalk or posterior lobe, but the anterior lobe was replaced by a loose fibrous tissue in which no remnants of parenchyma could be found histologically. The thyroid was red and small (7.2 grams). Microscopically the acini were small and lined by flat epithelium; they were full of colloid. There was moderate fibrosis, but there was only slight lymphoid infiltration. The adrenals were small (combined weight 2.7 grams). The capsule was thick. The cortex was very thin, rarely more than 0.15 mm., and contained some lipoid. The medulla appeared normal. The capsule was very thick. The ovaries and uterus were very atrophied. The thymus consisted only of thin laminae of epithelial cells with no lymphocytes. The pancreas showed very numerous islets which were within the normal range of size. The breasts showed very marked atrophy of acini.

The heart was of normal size (275 grams) but there was considerable atrophy of the liver (660 grams) and of the kidneys (combined weight 120 grams). The other findings were very gross atheroma of all arteries, particularly of the coronaries, ischemic fibrosis of the myocardium, much chronic cystitis, and a terminal acute pericarditis with bilateral pleural effusions. No gallstones were present.

*Comment.*—

This was a typical case of severe hypopituitarism, but its inclusion in the present series is open to question as the etiology is obscure. The condition at the second delivery was such as would be expected to produce necrosis in the anterior lobe, but there were no symptoms of hypopituitarism during the next few years. Thus, if a postpartum necrosis did occur, it can have been only a partial one. The amenorrhea did not begin until 8 years after the delivery and the full syndrome not until 23 years after delivery. It is very possible that some other pathological process developed in the pituitary when she was 34 and recurred when she was 49. This may or may not have been superimposed on a partial destruction by postpartum necrosis when she was 26. These are, however, mere speculations, and the pathological appearances at death were only those of a healed necrosis.

The extreme sensitivity of this patient to insulin is very characteristic of severe pituitary insufficiency. In these cases it is extremely dangerous to give more than 1.5 units of insulin for a tolerance test, and even with this dose great care is necessary.

### Summary

Ischemic necrosis of the anterior lobe of the pituitary is liable to occur when an obstetric patient has gross hemorrhage or shock at delivery. If the necrosis is a large one, the patient suffers from severe hypopituitarism for the remainder of her life.

This cause of chronic invalidism in women used to be reputed a rarity, because the clinical picture was not well recognized and also because the patients are mentally dull so that they do not seek medical attention. In the past few years it has become clear that the condition is relatively common.

A series of 9 cases which have been proved at autopsy during the past four years are recorded to illustrate the standard clinical and pathological pattern and its variations.

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## CHANGING CONCEPTS IN THE MANAGEMENT OF LABOR

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**I**N THE more than thirty years that have passed since Dr. George W. Kosmak became a founder and the first editor of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* the death rate in the United States for women in childbirth has fallen to less than one-sixth of its former figure. This has been accompanied by a significant but less striking drop in fetal mortality. A number of factors have caused such an amazing improvement in obstetrics that it surpasses the achievements in any other branch of medicine, and among them are many which concern the conduct of labor. The majority of these changes have been described in the *JOURNAL*, the editorial policy of which has been directed by Dr. Kosmak for so many years with such discrimination and sound judgment. They cover all three stages of labor and will be considered as they apply to each.

Today, if in competent hands, no woman need embark upon a labor which will prove impossible because of cephalopelvic disproportion. X-ray pelvimetry has far greater accuracy than the old instrumental methods. Moreover, serial roentgenograms during the course of labor enable the obstetrician to follow the progress of the presenting part and to decide whether accomplishment has been satisfactory or further advance is impossible or unlikely. Should dystocia be due to inertia alone and there be no cephalopelvic disproportion or malpresentation, the uterine-stimulating principle of pituitary extract given in minimal doses either intramuscularly or intravenously in high dilution in a large proportion of cases will improve progress to the point where delivery can be achieved either normally or by an easy forceps operation. The separation by Kamm and his co-workers in 1928 of the ecbolic and hypertensive principles has eliminated most of the potential dangers experienced earlier in the use of pituitary extract.

Thirty years ago cesarean section during labor carried a grave risk of peritonitis and the more labor had advanced the greater the risk. The obstetrician, therefore, once having committed his patient to a test of labor had no other recourse than to some type of pelvic operative delivery if progress should come to a halt. Today, if it should become evident that delivery through the natural passages is unlikely or inadvisable, the lower segment type of cesarean section may be employed and the patient protected against infection by the administration of the sulfonamides and antibiotics. If labor has been of long duration and sepsis is evident or suspected, the extraperitoneal operation affords an extra safeguard. Moreover, in well-conducted clinics, the use of these drugs, combined with improved methods of skin preparation and a technique of cleansing and sterilizing the hands that for the first time in the history of medicine

actually renders them free of bacteria, has practically eliminated puerperal sepsis whatever the method of delivery. At the present time manual dilatation of the cervix and accouchement forcé, as well as the high-forceps operation, have disappeared from good obstetric practice. These shocking and traumatizing operations were dangerous to the life and future health of the mother and infant, and their elimination has done much to remove the need for later plastic repairs.

A practitioner of thirty years ago might view the present frequent use of low forceps as somewhat radical, but results prove that given a reasonable amount of skill on the part of the operator it causes no more damage to the mother or infant than does normal delivery and it spares the integrity of the soft parts if accompanied by a suitable episiotomy. Moreover, it protects the infant from the cerebral damage that sometimes results from prolonged pressure against the pelvic floor. The same physician of an earlier era would probably be startled by the frequency with which at present labor is induced by rupture of the membranes, sometimes on good medical indications, sometimes to oblige the patient, but most often to suit the convenience of the doctor. While theoretically unsound, candor forces the admission that this procedure, if undertaken under proper circumstances, is seldom productive of harm. Our elderly friend, with some justification, might well be critical of the frequency of cesarean section, which varies from 2 to 6 per cent, depending on localities and clinics. Since the general mortality of this operation is in the vicinity of 0.5 per cent, until it becomes safer the obstetrician in a given case should always convince himself that it is really necessary and not merely an alternative way of delivering a baby.

Experience has shown that extreme conservatism in the conduct of the third stage of labor lowers the frequency of postpartum hemorrhage. It has been learned that this accident is best prevented by awaiting spontaneous separation of the placenta, and that the Brandt maneuver, in which it is gently urged from the lower uterine segment, even if it entails slight traction on the cord, is less likely to cause abnormal bleeding than is the more traumatizing Credé method whereby the fundus is vigorously squeezed and used as a piston to deliver the afterbirth. Moir's isolation of the active principle of ergot in 1932 has resulted in the manufacture of a standardized and reliable preparation of the drug which has introduced another factor of safety. Following the identification of the four blood groups by Jansky in 1907, the development of the citrate method of transfusion by Lewisohn in 1914, and the discovery of the Rh factor by Landsteiner and Weiner in 1940, transfusion has been rendered safe, simple, and, in most hospitals, readily available. It is probable that these contributions to our knowledge, together with the advent of the sulfonamides and antibiotics, have played the major parts in making childbirth the safe event that it is today.

The past thirty years have seen the extensive use of analgesic drugs, mostly the safer barbiturates, to assuage the pains of labor, and of an amnesic agent, scopolamine, to obliterate the memory of labor. In skilled hands such medica-

tion is highly successful; moreover, it permits a more extended test of labor and it even results in a lowered fetal mortality because, unaffected by importunities of the patient, the obstetrician is not tempted toward too early interference. During this time little real progress has been made toward improvements in the anesthetics used at delivery. Ether, alone or in combination with other agents, still remains the safest. Of late years there has been a disquieting tendency toward some form of spinal anesthesia in spite of the known fact that it is several times more dangerous than ether and that it is particularly so when given for cesarean section. The report of Kennedy covering numerous cases of late neurological damage following spinal anesthesia not only in obstetrics but also in general surgery has failed to alarm many obstetricians. Even if a patient escapes such a catastrophe there is at least a 10 per cent chance that soon after delivery she will suffer a troublesome headache which persists for days and for which no reliable means of relief or prevention has as yet been developed.

On the other side of the picture is the so-called "natural childbirth" of Grantly Dick Read and his disciples. There is nothing new about natural childbirth; it was the invariable rule up to 1847 when James Simpson first gave anesthesia to a woman in labor. Simpson was not without honor in his own country for he was made a baronet in 1866 and when he died four years later in Edinburgh a day of public mourning was decreed, the University and all the shops were closed, and thirty thousand fellow citizens attended his funeral. The Scottish women of that day liked anesthesia in childbirth; apparently they were not so psychologically developed as the American woman of the present. If a woman has an easy labor and it is accompanied by only slight or moderate pain there is no reason why she should not endure it without an anesthetic if she so desires, but if she does so there are no scientific data to prove that it establishes any special *rapprochement* between her and her infant or that she will love it any more deeply than if she were fast asleep when it was born. The Read regime entails a system of indoctrination during pregnancy of which the husband partakes; also there is a series of exercises hopefully designed to relax the muscles at the time of delivery. The husband does not take these exercises. One of the main objects of this prepartum briefing is to eliminate fear, which Read maintains intensifies the pains of labor. This may be true, but most obstetricians who have had large experiences with private patients have been impressed by the lack of apprehension with which they face labor. Possibly this is due to confidence in their doctors; if so it is part of their doctors' duty to inspire such confidence, but it should not require any special propaganda. It is a matter of record that Read administers anesthesia to those of his patients who desire it and he freely admits the fact. Moreover, about 5 per cent are delivered by cesarean section—a rather high incidence by conservative standards—and cesarean section cannot be regarded as "natural childbirth." However, the method has aroused considerable enthusiasm among the women who have been delivered under it, and there certainly can be no argument against it if it makes them happy.

The attitude of the capable obstetrician today toward his patients in labor is neither ultraconservative nor ultraradical; his willingness and ability to employ proper operative measures should the indications arise signify a guarded liberalism. David Humphreys Storer, who became professor of midwifery and medical jurisprudence at Harvard Medical School in 1854, described the correct conduct of labor as characterized by "patience and expectancy up to the proper time; prompt and fearless action when that time comes." That was good advice one hundred years ago and it is good advice now.



## A ROENTGENOLOGIC STUDY OF THE FILIPINO FEMALE PELVIS

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A COSTA-SISON<sup>1</sup> in 1914 was the first to study the pelvis of Filipino women, measuring the external diameters and the diameters of the pelvic inlet and outlet of 1,337 Filipino women. This work has been repeatedly quoted and is responsible for the often-made statement that the average Filipino pelvis is smaller than the average American pelvis and similar to the generally contracted pelvis of the white American. It also ascribes the easy labor and relative infrequency of cephalopelvic disproportion to the smaller size of the Filipino baby. In 1950, Manahan, Marquez, and Mariano<sup>2</sup> presented a preliminary roentgenologic evaluation of the pelves of 500 Filipino women. This work and the present report which is a continuation of the first are the only such studies on the pelves of Filipino women. The subjects were almost all private patients, the majority belonging to the middle and better half of the lower third in the socioeconomic group level. Selection was made only in that the patients were almost "pure" Filipinos, excluding those with an admixture of American, European, or Chinese blood within the last three generations.

The stereoscopic method of Hodges was employed in the study of the pelvic types and the measurement of the transverse diameters, and counter-checked by Snow's technique. Lateral plates were taken using Thoms' and Snow's procedures. Right at the outset we were posed with the problem of classification of the inlet. Lilienfeld, Treptow, and Dixon<sup>3</sup> and more recently Kaltreider<sup>4</sup> have demonstrated how varied the discrepancy could be in the interpretation of a single plate. To obviate this, each plate was separately studied by two observers, the pelvis classified and, when there was disagreement, the plate was then jointly judged until a final interpretation was agreed upon. No attempt was made to subdivide the major groups into subtypes and we were content to limit our classification of the inlet into "predominantly gynecoid" or "predominantly anthropoid" as the case turned out to be. We were also curious to see how the cases would be grouped using the Thoms classification.

### Pelvic Types

Table I shows the distribution into the four basic types of Caldwell and Moloy.

Of utmost interest is the high incidence of gynecoid (59.3 per cent) and anthropoid pelves (33.4 per cent) with an incidence of only 4.9 per cent of

android and 1.9 per cent of platypelloid pelves. How this compares with reports from abroad is presented in Table II which is modified from a table from Kaltreider.

TABLE I. CALDWELL-MOLOY INLET CLASSIFICATION OF Pelves, 875 UNSELECTED CASES

TYPE OF PELVIS	NUMBER	PERCENTAGE
Gynecoid (predominantly)	519	59.3
Anthropoid (predominantly)	292	33.4
Android (predominantly)	43	4.9
Platypelloid	17	1.9
Asymmetrical	4	0.5
Total	875	100.0

TABLE II. A COMPARISON OF FILIPINO PELVIC TYPES WITH AMERICAN

	GYNECOID	ANTHROPOID	PLATYPELLOID	ANDROID	OTHER
Western Reserve material	41.75%	32.0 %	2.15%	24.1 %	—
Sloane Hospital	50.6 %	22.7 %	4.4 %	22.4 %	1.8 %
Pettit, Garland, Dunn, Schumaker	51.0 %	18.0 %	5.0 %	21.0 %	5.0 %
Javert, Steele, Powlitis	50.0 %	13.0 %	9.0 %	28.0 %	—
Walsh, John G.	56.0 %	17.25%	3.0 %	23.75%	—
Kenny	54.46%	10.01%	2.81%	31.76%	9.38%
Manahan, Marquez, Mangay	59.3 %	33.4 %	1.9 %	4.9 %	0.5 %

It is this extremely high percentage of favorable obstetrical types and the very low occurrence of poor obstetric pelves that made us analyze the material using the more objective method of classification of Thoms which is based not only on the visual impression of the pelvic inlet but chiefly upon the relations of the lengths of the anteroposterior and transverse diameters to each other. This classification is not perfect as it is not a true index of pelvic capacity and it does not include the android variety. Table III shows how these 875 cases were finally grouped.

TABLE III. THOMS' INLET CLASSIFICATION OF Pelves, 875 UNSELECTED CASES

TYPE OF PELVIS	NUMBER	PER CENT
Mesatipellic	372	42.5
Brachypellic	256	29.2
Dolichopellic	239	27.3
Platypellic	4	0.5
Asymmetrical	4	0.5
Total	875	100.0

As in the Caldwell and Moloy classification, we find a high incidence of obstetrically favorable pelves.

### Pelvic Measurements

#### *The Pelvic Inlet.*—

Tables IV, V, and VI give the dimensions of the diagonal conjugate, the obstetrical conjugate, and the transverse diameter of the pelvic inlet.

We find our figures at variance with the clinical measurements of Acosta-Sison<sup>5</sup> on 1,500 Filipino women. Where she gives the dimension of the diagonal

TABLE IV. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF THE DIAGONAL CONJUGATE (DC) OF 873 FILIPINO PELVES

DIAGONAL CONJUGATE (DC) IN CM.	NUMBER OF CASES
9.0- 9.4	1
9.5- 9.9	0
10.0-10.4	5
10.5-10.9	18
11.0-11.4	38
11.5-11.9	74
12.0-12.4	111
12.5-12.9	130
13.0-13.4	171
13.5-13.9	144
14.0-14.4	107
14.5-14.9	40
15.0-15.4	25
15.5-15.9	6
16.0-16.4	2
16.5-16.9	1
Total	873
Mean —13.10	Q <sub>1</sub> (25%)—12.37
Median —13.17	Q <sub>2</sub> (50%)—13.17
Mode —13.00	Q <sub>3</sub> (75%)—13.87

TABLE V. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF THE OBSTETRICAL CONJUGATE OF 859 FILIPINO PELVES

OBSTETRICAL CONJUGATE (OC) IN CM.	NUMBER OF CASES
8.0- 8.4	1
8.5- 8.9	3
9.0- 9.4	10
10.0-10.4	69
10.5-10.9	89
11.0-11.4	138
11.5-11.9	166
12.0-12.4	164
12.5-12.9	118
13.0-13.4	58
13.5-13.9	31
14.0-14.4	8
14.5-14.9	2
15.0-15.4	2
Total	859
Mean —11.81	Q <sub>1</sub> (25%)—11.11
Median —11.84	Q <sub>2</sub> (50%)—11.84
Mode —12.00	Q <sub>3</sub> (75%)—12.50

TABLE VI. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF THE TRANSVERSE DIAMETER OF 875 FILIPINO PELVES

TRANSVERSE DIAMETER (T) IN CM.	NUMBER OF CASES
9.0- 9.4	1
9.5- 9.9	2
10.0-10.4	14
10.5-10.9	23
11.0-11.4	79
11.5-11.9	149
12.0-12.4	238
12.5-12.9	186
13.0-13.4	124
13.5-13.9	42
14.0-14.4	15
14.5-14.9	2
Total	875
Mean —12.35	Q <sub>1</sub> (25%)—11.83
Median —12.36	Q <sub>2</sub> (50%)—12.36
Mode —12.50	Q <sub>3</sub> (75%)—12.90

conjugate as 12.0 cm., we find it to be 13.17 cm. Where her obstetrical conjugate is 10.8, we find our measurement to be 11.84 cm. There is near agreement in the measurement of the transverse diameter of the inlet which she gives at 12.13 cm. and which we found to be 12.36 cm.

We found it difficult to obtain roentgenologic measurements of the American pelvis due to our still poor library facilities. However, comparing our figures with those of Francis,<sup>6</sup> who compiled the more usual measurements from a number of sources, we find to our surprise that the average anteroposterior diameter in our patients is not smaller than that of the average American pelvis. Actually, it is longer. Francis states that the obstetrical conjugate is 11.0 cm., ours is 11.84 cm. The diagonal conjugate is 12.5 cm. and ours is 13.17 cm. The transverse diameter of the inlet of Filipino women is smaller, as our figure is 12.36 cm., while the average measurement as compiled

TABLE VII. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF INTERSPINOUS DIAMETER

INTERSPINOUS DIAMETER (IS) IN CM.	NUMBER OF CASES
7.0- 7.3	1
7.4- 7.7	4
7.8- 8.1	8
8.2- 8.5	23
8.6- 8.9	39
9.0- 9.3	112
9.4- 9.7	195
9.8-10.1	176
10.2-10.5	164
10.6-10.9	56
11.0-11.3	57
11.4-11.7	24
11.8-12.1	4
12.2-12.5	3
12.6 and over	1
Total	867
Mean — 9.95	Q <sub>1</sub> (25%)— 9.74
Median — 9.92	Q <sub>2</sub> (50%)— 9.92
Mode —10.00	Q <sub>3</sub> (75%)—10.43

TABLE VIII. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF ANTEROPOSTERIOR DIAMETER OF THE MIDPLANE OF 873 FILIPINO PELTS

ANTEROPOSTERIOR DIAMETER OF THE MIDPLANE (APM) IN CM.	NUMBER OF CASES
8.5- 8.9	1
9.0- 9.4	6
9.5- 9.9	20
10.0-10.4	67
10.5-10.9	100
11.0-11.4	186
11.5-11.9	139
12.0-12.4	165
12.5-12.9	86
13.0-13.4	59
13.5-13.9	32
14.0-14.4	7
14.5-14.9	4
15.0-15.4	1
Total	873
Mean —11.75	Q <sub>1</sub> (25%)—11.07
Median —11.70	Q <sub>2</sub> (50%)—11.70
Mode —12.00	Q <sub>3</sub> (75%)—12.41



by Francis is 13.0 cm. This anteroposterior lengthening and comparative transverse narrowing is, however, in keeping with our findings of a high occurrence of anthropoid and gynecoid pelves and a much lower incidence of platypelloid and android pelves than is found in American women.

*The Midpelvis and Outlet.*—

The dimensions of the midpelvis and outlet are given in Tables VII, VIII, IX, X, and XI.

TABLE IX. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF THE POSTERIOR SAGITTAL (PSM) OF THE MIDPLANE OF 874 FILIPINO PELVES

POSTERIOR SAGITTAL OF THE MIDPLANE (PSM) IN CM.		NUMBER OF CASES
1.5-1.9		1
2.0-2.4		4
2.5-2.9		23
3.0-3.4		99
3.5-3.9		165
4.0-4.4		252
4.5-4.9		166
5.0-5.4		103
5.5-5.9		34
6.0-6.4		18
6.5-6.9		7
7.0 and over		2
Total		874
Mean	—4.33	Q <sub>1</sub> (25%)—3.78
Median	—4.29	Q <sub>2</sub> (50%)—4.29
Mode	—4.00	Q <sub>3</sub> (75%)—4.84

TABLE X. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF INTERTUBER-ISCIAL DIAMETER (IT) OF 875 FILIPINO PELVES

INTERTUBER-ISCIAL DIAMETER (IT) IN CM.		NUMBER OF CASES
7.0- 7.4		1
7.5- 7.9		0
8.0- 8.4		2
8.5- 8.9		12
9.0- 9.4		42
9.5- 9.9		78
10.0-10.4		135
10.5-10.9		174
11.0-11.4		173
11.5-11.9		128
12.0-12.4		76
12.5-12.9		32
13.0-13.4		15
13.5-13.9		6
14.0-14.4		0
14.5-14.9		1
Total		875
Mean	—10.98	Q <sub>1</sub> (25%)—10.31
Median	—10.99	Q <sub>2</sub> (50%)—10.98
Mode	—11.00	Q <sub>3</sub> (75%)—11.65

The occurrence of a longer anteroposterior diameter and a relative narrowing of the transverse diameter is also found in the midpelvis. Our measurement of the bispinous diameter is 9.92 cm. as compared to 10.5 cm. in the American pelvis. Our anteroposterior diameter of the midplane is 11.7 cm. as contrasted with Francis' figure of 11.5 cm. The outlet measurements are in-

teresting, too, in that, while the biischial measurements are almost the same—11.0 cm. for the American and 10.98 for our series—the posterior sagittal is given as 9.5 cm. for the American pelvis and ours is 7.28 cm. This explains the clinical experience of one of us (C. P. M.) who invariably employs a median episiotomy for American patients but finds the perineum of the Filipino patients short and has usually to resort to a mediolateral episiotomy in delivering primiparous Filipino patients.

TABLE XI. FREQUENCY DISTRIBUTION OF X-RAY MEASUREMENTS OF POSTERIOR SAGITTAL OF THE OUTLET

POSTERIOR SAGITTAL OF OUTLET (PSO) IN CM.	NUMBER OF CASES
4.0- 4.4	6
4.5- 4.9	5
5.0- 5.4	24
5.5- 5.9	55
6.0- 6.4	107
6.5- 6.9	142
7.0- 7.4	173
7.5- 7.9	146
8.0- 8.4	109
8.5- 8.9	50
9.0- 9.4	37
9.5- 9.9	10
10.0-10.4	8
10.5-10.9	2
11.0-11.4	0
11.5-11.9	1
Total	875
Mean —7.31	Q <sub>1</sub> (25%)—6.58
Median —7.28	Q <sub>2</sub> (50%)—7.28
Mode —7.50	Q <sub>3</sub> (75%)—7.55

### Comment

This roentgenologic study of the Filipino female pelvis demonstrates a rather high incidence of favorable obstetric types among Filipino women and a relatively low incidence of android and flat pelvis as compared to American women. Our roentgenologic measurements are in disagreement with those obtained clinically by Acosta-Sison. We have counterchecked our findings using Snow's technique and found general agreement between the two. The accuracy of roentgenologic measurement is generally accepted while clinical measurements are fraught with error because of the mechanical difficulty of the procedure, and the intervention of the soft tissue, the thickness of which may vary with each patient. In terms of dimensions alone, we find our average anteroposterior diameter of the inlet and midpelvis actually longer than the American, although the transverse diameters of both inlet and midpelvis are slightly narrower. Del Mundo,<sup>7</sup> who has recently measured Filipino babies, gives the average weight of the Filipino baby in this type of patient as 7.2 pounds, which is only slightly less than that of the white American baby (7.48 pounds). Time did not allow us to do this evaluation for our own series.

In view of the findings regarding the pelvic architecture and the measurements obtained roentgenologically, we cannot agree with Acosta-Sison's conclusion that "the average normal measurements (of the Filipino pelvis) are

similar to those of the generally contracted pelvis of the white American." Rather, we find that the comparative rarity of the flat and especially of the android types makes the Filipino pelvis obstetrically almost ideal and may be the explanation for the easy labor and infrequency of cephalopelvic disproportion among Filipino women. This, and the high incidence of gynecoid and anthropoid pelvises, even in the face of the relative narrowing of the transverse diameters, rather than the smaller size of the Filipino baby accounts for the lack of mechanical dystocia, since it has been established that favorable pelvic architecture more than counterbalances moderate shortening of the diameters.

Clinically, the longer anteroposterior diameters and the slight narrowing of the transverse diameter at the inlet and midpelvis have been associated with a high incidence of occipitoposterior presentation. In our experience, dystocia, when it occurs, is more often met at the midpelvis rather than at the inlet. This, again, is more in keeping with the large number of anthropoid and gynecoid pelvises, the transverse narrowing at the midpelvis, and the general narrowing of the outlet. A composite chart of the different measurements is presented in Table XII.

TABLE XII. SUMMARY

PELVIC MEASUREMENT OR INDEX	CENTERING VALUES IN CENTIMETERS			VALUES IN CENTIMETERS				
				LOWEST	25 PER- CEN- TILE	50 PER- CEN- TILE	75 PER- CEN- TILE	HIGH- EST
	MEAN	MEDIAN	MODE					
<i>Inlet.—</i>								
Obstetrical conjugate (OC)	11.81	11.84	12.00	8.1	11.11	11.84	12.50	15.2
Transverse diameter (T)	12.35	12.36	12.50	9.0	11.83	12.36	12.90	14.7
Diagonal conjugate (DC)	13.10	13.17	13.00	9.2	12.37	13.17	13.87	16.9
Weinberg and Scadron's sum (OC & T)	24.07	24.15	24.10	19.1	23.03	24.15	25.16	28.9
Mengert's area %	99.97	100.04	103.00	61.0	91.29	100.24	109.06	144.0
<i>Midplane.—</i>								
Anteroposterior (APM)	11.75	11.70	12.00	8.8	11.07	11.70	12.41	19.1
Posterior sagittal (PSM)	4.53	4.29	4.00	1.6	3.78	4.29	4.84	9.5
Interspinous diameter (IS)	9.95	9.92	10.00	7.0	9.46	9.92	10.43	13.8
Weinberg and Scadron's sum (IS & PSM)	14.19	14.14	14.40	10.2	13.40	14.14	15.00	19.1
Mengert's area %	93.18	92.42	94.00	60.0	85.06	92.42	100.94	133.0
<i>Outlet.—</i>								
Intertuberous ischial diameter (IT)	10.99	10.98	11.00	7.3	10.31	10.98	11.65	14.5
Posterior sagittal (PSO)	7.31	7.28	7.50	4.0	6.58	7.28	8.00	11.6
Thoms' outlet value (IT & PSO)	18.20	18.17	18.50	13.6	17.13	18.17	19.28	23.6

### Conclusions

1. The pelvic architecture of Filipino women presents a higher incidence of gynecoid and anthropoid pelvises, and fewer platypelloid and android pelvises than that of American women.

2. The average anteroposterior diameters of the inlet and midpelvis are actually longer than average measurements given for American women.

3. There is narrowing of the transverse diameters of both inlet and mid-pelvis when compared with figures for American women.

4. The high incidence of good obstetric types, anthropoid and gynecoid, more than offsets this transverse narrowing and this high incidence of architecturally good pelvises more than the relatively smaller size of Filipino babies is responsible, we believe, for the easy labors and infrequency of cephalopelvic disproportion in Filipino women.

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## THE TWO HUNDRED YEARS' TEACHING OF THE MECHANISM OF LABOR

### A Medico-historical Sketch

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TODAY the mechanism of labor is regarded as a basic topic in obstetrics, and in all elementary texts on the principles of this science one finds a chapter or a section reserved for a description of the changes in position and posture imposed upon the child by the process of engagement and expulsion. It is remarkable that facts now considered fundamental to obstetrics have not been known by the professional world more than about 200 years.

Before the appearance of Smellie's<sup>1</sup> *A Treatise on the Theory and Practice of Midwifery*, the conception of what actually takes place in parturition was largely conjectural, founded as it was mainly on tradition and authority and not on unprejudiced observation to any degree comparable with Smellie's presentation.

In the following I shall try to outline some features of the development of the doctrines regarding the mechanism of labor from Smellie's time to our day. My survey will be based on short accounts of the contributions of some of the leading authors and the results of later research work, and I shall confine myself to the descriptive side of the matter and to some features of the process of parturition, which are still differently described in modern presentations.

Before Smellie, during the later seventeenth and the first half of the eighteenth centuries, obstetrics was certainly not a neglected study and new domains were conquered in fields of considerable practical and theoretical importance. The knowledge of the actual process of motion in parturition remained, however, incomplete. A good picture of the state of the knowledge and the ideas ruling at the time just before the appearance of Smellie's epoch-making contribution is obtained by reference to the work of Fielding Ould<sup>2</sup> of Dublin. As we shall see, Ould's views on some matters were completely traditional, but, at the same time, he anticipated coming developments on a very essential point.

Fielding Ould was the successor of Mosse, the first master of the Rotunda Lying-in Hospital of Dublin. Ould was born about 1710 and died 1789. His mastership lasted from 1760 to 1766. He was knighted in 1760. His literary contribution to be taken into consideration here is *A Treatise of Midwifery in Three Parts, Dublin 1742*.

Most of the obstetricians of the seventeenth century believed that the fetus regularly turned from a position with the breech at the pelvic inlet to

the cranial presentation during the later months of pregnancy, this idea being an inheritance from Hippocratic medicine. During the beginning of the eighteenth century this classic doctrine of the somersault was still good orthodoxy. In Ould's presentation it reappeared in a rather fanciful form, in that he held that this change of the child's position occurred in the beginning of labor as a result of the pressure effect of the fundus uteri on the back of the head.

What is new and important in Ould's exposition is the description of the position of the head in the pelvis. In his *Treatise* he says: "When a child presents itself naturally, it comes with the head foremost, and (according to all authors that I have seen) with its face towards the sacrum of the mother, so that when she lies on her back, it seems to creep into the world on its hands and feet. But here I must differ from this description in one point which at first sight may probably seem very trivial: The breast of the child does certainly lie on the sacrum of the mother, but the face does not; for it always (when naturally presented) is turned either to the one side or the other, so as to have the chin directly on one of the shoulders."

Ould's explanation of the head's passing the pelvis in the transverse position is its oblong shape and the elliptical form of the pelvic cavity, "from one to the other hip."

The supposed turned posture of the head, in relation to the trunk, with the chin on one of the shoulders is a curious feature of Ould's presentation. He did not mention the fact that the fetal head becomes turned during parturition from a transverse position in the inlet to a position with the longer diameter in, or almost in, the sagittal plane of the pelvis in the genital outlet, and his expositions are not at all comparable to Smellie's as regards completeness and correctness. Nevertheless, his name has a place in the history of obstetrics because he is the first author who really touched on the topic called later the mechanism of labor.

Smellie's *A Treatise on the Theory and Practice of Midwifery* is rightly regarded as one of the outstanding classics of the field of obstetrics. The first edition was dated London, 1752, but was actually issued late in 1751, and his *Anatomical Tables*,<sup>3</sup> constituting a most instructive complement to the treatise, was published in 1754.

Smellie opposed the old doctrine of the somersault, performed by the fetus before or during parturition, and maintained "that the head for the most part turned down to the lower part of the uterus from conception to delivery." In his work a very complete description of the movement and positions of the fetal head is given and a study of the *Treatise* together with the *Anatomical Tables* discloses that he not only had a very detailed knowledge of the normal and usual mechanism of labor but that he also knew the essentials of the less common variants such as the occipitoposterior and the face presentations. His description of the usual mechanism was a revolutionary accomplishment and, actually, it is in almost complete agreement with what would be encountered in a modern textbook.

Because of the completeness and correctness of Smellie's presentation of the topic, it is not necessary to give here any account of his description, the aim of the present article being simply the elucidation and discussion of the mechanism of labor from the historical point of view.

These are the points mainly to be taken into consideration in the short survey to follow:

1. The usual position of the fetal head in the pelvic entrance.
2. The flexional movement of the head supposed to take place during engagement and descent.
3. The state of synclitism or asynclitism exhibited by the head in early engagement and during descent.

Regarding the position of the head in the pelvic inlet Smellie's own description is this: "When the head first presents itself at the brim of the pelvis, the fore-head is to one side, and the hind-head to the other, and sometimes it is placed diagonal in the cavity." As stated, he held that the transverse position of the head was the usual one in the inlet, but he had not failed to observe that it sometimes enters the pelvis in an oblique position. Smellie explained the tendency of the head to take up a transverse position in early engagement as a consequence of the oval shape of the head and the spatial conditions of the pelvic inlet. As to the latter his description was as follows: "The brim or upper part of a well-shaped pelvis represents a kind of imperfect oval, or something that approaches a triangular figure. If we consider it as an oval, the long axis passes from side to side. . . ." This is no poor description but it has been criticized by later authors on the grounds that Smellie did not take the oblique diameters into consideration, which latter were supposed to be longer than the transverse one in the normal case.

In most modern presentations of the mechanism of labor, a distinct flexional movement of the head is mentioned and claimed to constitute a characteristic link in the process of engagement and descent.

Smellie did not mention any flexional movement of the head during engagement and descent, but he said that "the crown or vertex is the first part that is pressed down" and that thereby "the face is always turned upwards." The last expression could perhaps be understood in such a way that it refers to some turning movement. However, if all his utterances on the mechanism of engagement and descent are taken into consideration, and if one reads his deliberations unbiased by the later development of obstetrical teaching I think one must be convinced that this interpretation is false. In order to support this opinion I shall quote from the section of the *Treatise* dealing with the management of women in natural labor: "When the head rests at first above the brim of the pelvis, and is not far advanced, the fontanel may be plainly felt with the finger, commonly towards the side of the pelvis. . . ." Some few lines farther on his description runs as follows: "When the vertex is come lower down, the sagittal suture only is to be felt; because, as the hind head descends in the pelvis, the fontanel is turned more backwards to the side, or towards the concavity of the sacrum." These

quotations show that he was of the opinion that the disappearance of the anterior fontanel from the field which can be reached by palpation is due to the internal rotation and there is nothing to indicate that he discerned anything like a flexional movement of the head.

In his description of the normal position of the head in the inlet Smellie did not mention anything about the obliquity of the head which later was termed asynclitism, but this feature is well demonstrated in two of the tables of the atlas,<sup>3</sup> Table IX showing posterior asynclitism in a case before parturition and Table XII exhibiting the same obliquity in a case during parturition.

During the later part of the eighteenth century and the beginning of the nineteenth, obstetrical teaching was greatly influenced by the writings of Solayrès de Renhac<sup>4</sup> and Saxtorph,<sup>5</sup> and thereby ideas were introduced and generally accepted which differed from Smellie's views on the mechanism of engagement. The essays of these authors, which will be considered here, were written in Latin but both are available in German translations. Selected parts are translated into English and included in Leishman's<sup>7</sup> monograph on the mechanism of parturition.

François Louis Joseph Solayrès de Renhac (1737-1772) got his medical education at the University of Montpellier and graduated as Doctor medicinæ at this university in 1767. From 1767 he was active as a practitioner of obstetrics and as a lecturer in Paris. His main literary contribution, *Dissertatio de partu viribus maternis absoluto*, etc., was issued in Paris in 1771 as a thesis for a professorship at the *École pratique* and for membership in the *Collège de Chirurgie*. The public defense of his treatise was prevented by the author's illness and Solayrès died from pulmonary tuberculosis April 3, 1772. A translation of the dissertation into the German language was issued in Frankfurt a. M. in 1835.

Solayrès described 6 normal positions of the fetal head in the pelvic inlet. If, for the sake of convenience, we use a modern nomenclature these positions are: (1) occiput direct anterior, (2) occiput direct posterior, (3) occiput anterior and to the left, (4) occiput anterior and to the right, (5) occiput posterior and to the left, and (6) occiput posterior and to the right.

The transverse position in the inlet was not regarded by him as a normal and typical one. In the description of the course of movement Solayrès disclosed considerable ability as an observer, but his presentation is less simple and less clear than Smellie's.

Without any doubt Baudelocque's<sup>8</sup> important literary and teaching activities contributed greatly to making Solayrès' contributions known and appreciated by the professional world. Baudelocque attended Solayrès' lectures in Paris and was greatly influenced by his teacher, whom he mentions in his writings with expressions of deep affection and gratitude. Baudelocque adopted Solayrès' classification of the positions of the fetal head in the pelvic entrance, developed his ideas, and gave the whole presentation of the mechanism of labor a clear and concise form of great educational value.

Matthias Saxtorph (1740-1800) studied at the University of Copenhagen and became Doctor medicinæ in 1771. He was subsequently appointed Professor designatus of medicine



in 1773, Accoucheur at the State Maternity Hospital of Copenhagen in 1787 and Professor ordinarius in 1795. Saxtorph was a productive author and much attention was paid to his publications, especially by the German obstetricians. His teacher of obstetrics, Christian J. Berger, was the first professor of obstetrics at the University of Copenhagen, and, though not very productive as an author, he was a fine obstetrician and an excellent teacher. It is obvious that Saxtorph's earlier writings were inspired by Berger. Saxtorph's most important work on obstetrics was his dissertation for the Doctor's degree, *Dissertatio inauguralis de diverso partu ob diversam capitis ad pelvim relationem mutuam*, Copenhagen, 1771. This work was translated into the German language and is contained in Saxtorph's *Gesammelte Schriften*, edited by his son, J. S. Saxtorph and P. Scheel and published in Copenhagen in 1804.

As mentioned above, Saxtorph's dissertation was printed in 1771, the same year as Solayrès published his treatise. The ideas of these two authors are akin to each other but there is nothing to indicate any mutual influence or dependence. Saxtorph took Smellie's work into critical consideration, and objected especially to Smellie's views on the inlet mechanism and the shape properties of the pelvic inlet. Saxtorph held that the oblique diameter of the pelvic entrance is longer than the transverse one and he believed that the head nearly always enters the pelvis in an oblique diameter as a consequence of these spatial conditions. He gave a detailed description of the normal mechanism of labor essentially in conformity with modern concepts. In his exposition he mentioned the increase in flexion of the head occurring during descent and connected the whole course of movement with the space available in the different parts of the bony pelvis. The whole presentation bears witness to observational skill and a technical perfection which is in advance of his day.

For a long time thereafter ideas and concepts seemed to be settled and the perhaps not very important but nevertheless very real discrepancies from Smellie's presentation were soon regarded as improvements and corrections on the latter. As late as 1876 The New Sydenham Society of London issued a new edition of Smellie's *Treatise* and this edition was supplied with excellent and very instructive commentaries by Alfred H. McClintock. In discussing Smellie's descriptions and ideas on the mechanism of labor McClintock says, "Little of what Smellie described and laid down has been found wrong, and not very much has been added to it, except in regard to details, and to the causation of the various movements of the head in partu. His greatest error, perhaps, was the assertion that the fetal head as a rule enters the brim in its transverse or bis-iliac diameter, the forehead being at one side and the occiput at the other."

It was not until x-ray opened new possibilities for objective registration of the position of the head that new light was shed on this question. The most important radiological studies of the normal and pathological mechanism of labor have been performed by Caldwell and Moloy and their co-workers at the Sloane Hospital of New York. In 1934 Caldwell, Moloy, and D'Esopo<sup>9</sup> gave an account of a roentgenological investigation dealing with the mechanism of engagement as studied in 200 unselected cases. The transverse position in the inlet occurred in 60 per cent, the anterior and posterior

position each in about 20 per cent of their cases. In the group tabulated as in transverse position some cases are included which the authors designated transverse position tending to anterior or posterior position, respectively. This investigation must be said to have confirmed definitely Smellie's original description. The truth is simply that the mechanism of engagement is more variable than most of the authors after Smellie would admit and that the transverse position of the head in the pelvic inlet is more usual than any of the other variants.

The next feature to be considered is the flexional movement of the head which is supposed to occur during engagement and descent. Smellie's utterances regarding the flexion are not completely clear, but, as stressed before, the only natural interpretation seems to be that he regarded flexion as a position held by the head during engagement rather than as a turning movement. Solayrès mentioned the approach of the posterior fontanel to the center of the pelvis during the descending movement of the head in the occipitoanterior position, and Saxtorph described how the occiput is lowered and the forehead turned toward the chest as labor progresses. Baudelocque, finally, described three successive turning movements of the head during parturition, "flexion en avant," "mouvement de pivot," and "flexion en arrière." After Baudelocque and up to modern time this manner of presentation has prevailed.

However, time and again views opposite to those mentioned above have been advanced. Van Solingen<sup>10</sup> (1801), Werth<sup>11</sup> (1888), Webster<sup>12</sup> (1903), and Eden<sup>13</sup> (1908) can be mentioned as authors who believed that no flexional movement takes place during engagement and descent, but that the position of the head with regard to flexion is constant or nearly so from the start of labor until the internal rotation begins.

When speaking of the state of flexion of the child's head we must discriminate between the meaning of this term when used in order to characterize the fetal attitude and when used with reference to the position of the head itself. Actually, it has been used and still is used in routine clinical work in the latter sense, notwithstanding the fact that, conceptually, flexion is a postural property. The fact that the word flexion is also employed to designate a distinct movement of the head assumed to be induced during engagement and descent further increases the confusion.

As thoroughly described first by Karl Schröder<sup>14</sup> (1886), the spinal column of the child becomes straightened out as labor progresses. This change in attitude, mentioned also by Caldwell and his co-workers, implies an anterior bending of the child's head in relation to the trunk.

Quite another question is whether the head really makes a turning movement during engagement in the sense of changing its presenting part. Nowadays, this seems to be the belief of all authors who try to give a consistent description of the mechanism of labor, and in modern textbooks it is the uniform custom to discern a real flexional movement by which the occiput becomes lowered and the circumference presented diminished.

In a monograph on the mechanism of labor issued this year I<sup>15</sup> have discussed this topic more fully and presented the results of roentgenological examinations, aiming at an elucidation of what actually takes place during delivery as regards the child's posture and the position of the head. Here my conclusions are summarized briefly and the reader is referred to the publication just mentioned for documentation:

1. As a consequence of the stretching of the fetal spine during delivery and of the fact that its cranial part is often even bent into a lordotic curvature, the angle between the cervical column and the base of the skull is diminished. In this sense an anterior bending of the head is a regular and characteristic feature of the mechanism of labor in the case of vertex presentation.

2. On the contrary, in the sense of a rotational movement of the head, flexion is usually not induced during engagement and descent.

3. In most cases the head is relatively stable at the brim and the occiput definitely lowered into the pelvic entrance before labor begins. In such cases descent proceeds in a pronouncedly stable position of strong flexion until the internal rotation occurs and thereby deviation of the occiput to the front is brought about.

4. Pronounced flexional movement takes place only in cases where the occiput, before labor, is not lowered into the pelvic inlet, but instances of this kind are in the minority.

The above statements actually confirm Smellie's description of the mechanism of engagement if his expositions are to be understood in the way I have explained them in the beginning of this study. Even in the case of flexion I believe that Smellie's views were nearer the truth than those of most of the authors after him.

In 1819 F. C. Nægele<sup>16</sup> of Heidelberg published a famous essay on the mechanism of labor. It contains a detailed description of the positions and movements of the infant's head during parturition and some of Nægele's observations were new and of unquestionable value. Such observations are the usual transition of the primary occipitoposterior positions into occipito-anterior by means of long internal rotation and the common oblique position of the head when it passes through the genital outlet.

The most startling point in Nægele's presentation was the assertion that the head usually enters the pelvis in a strongly oblique position in which the anterior parietal bone constitutes the presenting part. This obliquity has later been termed anterior or Nægele's asynclitism. It seems that Nægele's views on the inlet mechanism were widely accepted at first, but it can be definitely stated now that on this point his descriptions were at fault. His error was probably due to a false notion of the direction of the descending movement of the head through the pelvic entrance and to his failure to understand the consequences which the different directions of the upper and the lower birth canal must have for the findings in palpatory examination (cf. the

critical scrutiny of Nægele's doctrine presented by Leishman in his monograph).

The obliquity called posterior asynclitism was first thoroughly described and examined by Litzmann<sup>17</sup> (1871) and is therefore often termed Litzmann's obliquity. Here the posterior parietal bone occupies the pelvic inlet and the sagittal suture is displaced anteriorly. Litzmann found this obliquity in about 10 per cent of the cases of contracted pelvis and not exclusively in the instances of flat, contracted pelvis. In women with normal pelves, Litzmann observed posterior obliquity in 1.2 per cent. He regarded this position as a "fehlerhafte Einstellung," though not entailing a serious prognosis in cases where the pelvis is of normal size and proportions.

Pinard and Varnier<sup>18</sup> (1892) described the normal mechanism of engagement and descent in a way which differed considerably from earlier views. According to these authors the usual and normal mechanism is such that the head enters the pelvis in a position of posterior asynclitism. By means of lateral flexion this position changes during descent and when the head is low in the pelvis its position is regularly brought over into anterior asynclitism.

In their comprehensive radiological studies Caldwell and his associates largely confirmed the description given by Pinard and Varnier. According to Caldwell, Moloy, and D'Esopo<sup>9</sup> the inlet mechanism varies, but in cases where the occiput is to the side of the pelvis posterior asynclitism is the common position in early engagement. Moreover, these authors found that, during further descent, the long axis of the head swings downward and backward, this movement resulting in anterior asynclitism of a lesser degree, when the head is low in the pelvis.

It seems to me that the study of the historical development of the doctrines regarding the mechanism of labor during the 200 years after Smellie can only enhance our admiration of the man and his work. It is certainly true, as has been said about him, that little of what he described and laid down has been found wrong, but it should be added that some of the alleged corrections and improvements have turned out to be errors. His assertion was correct that the common position of the head in the inlet is the transverse one, his conceptions of the position of the head during descent were most likely true, and the asynclitic position of the head during early engagement is, if not expressly described by him, nevertheless reproduced in his tables.

In glancing at the few pages of the *Treatise* which concern the mechanism of labor one is struck by the simple and modest style which Smellie used to present this basic topic. It seems that he was himself hardly aware of the deep cleft between his own descriptions and those of the big authorities some few years before. At any rate he certainly did not put his own accomplishments into the limelight and his exposition is always objective and realistic, a true expression of the deep candor of mind which was characteristic of this great man.



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## FORCEPS DELIVERY

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THE proper place of the forceps operation in obstetric practice has been much discussed over the years with considerable criticism as well as praise. Some of the criticism was undoubtedly justified, due largely to a misinterpretation of the functions of forceps and a misunderstanding of the proper technique to be used, as well as to a lack of opportunity for residents in training to become familiar with the proper use of forceps. On the other hand, a considerable number of the consequences for which forceps were blamed were the results of labor itself and even of a lack of timely interference with forceps. To establish a proper balance between the advantages and the shortcomings, it is necessary to consider what procedures led to harm to mother or child or to both and by eliminating them bring about rational indications for the operation and continue to consider it as one of the most valuable assets of obstetric practice. The most dangerous operation as it was performed several decades ago and unfortunately occasionally today was that of high forceps, an operation which frequently brought about disastrous results. It is now quite generally conceded that cesarean section is a preferable operation. Fortunately, the high forceps operation is almost never performed today and therefore forceps deliveries are limited, as they should be, to cases in which the fetal head is in the pelvic cavity and preferably low down. It would be well if the physician while using forceps would think less of them as instruments of force and concentrate on making the delivery easier by removing, as far as is possible, any factors which either cause unusual resistance or make necessary unwarranted traction force. It probably would be better if such things as dilatation and compression were omitted from the usual list of functions of the forceps. These are things to be avoided as far as possible rather than real functions of the forceps. Two outstanding causes of difficulty in forceps deliveries are the resistance of an insufficiently dilated cervix and an abnormal position such as the occipitoposterior position and transverse arrest. I believe that one of the chief causes of bad results is the attempt to deliver through an undilated os using the child's head as a dilator. Fortunately this is not done today as often as it was formerly. Credit for this, to a large extent, is due to the use of sedation and analgesia in the first stage of labor. Without this relief to the patient the doctor was tempted, often against his better judgment, but under pressure by the family to "do something," to deliver before he should. When the patient is given sufficient relief by analgesia and time is allowed, it is surprising in what a large percentage of cases there will be spontaneous progress to full dilatation. If in the occasional emergency it seems necessary to deliver with forceps when there is still a resistant ring of cervix this

should be dilated, as far as possible, manually or if necessary by Dührssen's incision so that the baby's head is the dilator to the least possible extent. The following incident is a good illustration of the resistance of the cervix and the pressure to which the child's head would be subjected. A doctor came out of the delivery room looking thoroughly fatigued and said, "I have been pulling against that tough cervix for two hours and am all in." Undoubtedly the cervix has been one of the most troublesome factors in labor and its complete dilatation often requires a great deal of time and much patience on the part of the physician but the forceps operation should not be primarily considered until the second stage of labor. The removal of resistance should also apply to the entire birth canal, being brought about by the so-called "ironing out," this very commonly supplemented by episiotomy.

One very common example of the use of unnecessary traction force is seen in the case of the occiput posterior position. To obviate this the head should always be rotated to a normal anterior position before traction is made. I am definitely opposed to any traction upon the head while in the posterior position and never have deliberately delivered a head in this position. The amount of traction force necessary to deliver a head in an anterior position is only a fraction of the force necessary in the posterior position. Probably most obstetricians who have been called in consultation have had an experience similar to this. Two doctors had each in turn attempted to deliver by forceps with no advance of the head. The forceps had slipped off, cutting the vaginal wall. Examination showed the position to be an occiput posterior. When the head was rotated by forceps to an anterior position delivery was accomplished with remarkably little traction force.

When on service at the Cleveland Maternity Hospital, Dr. Burdett Wylie developed a tractionometer which was inserted into the traction rod of the Bill traction handle. This registered in kilograms the amount of force used. I relate merely one demonstration of force needed as recorded by the instrument. In a case of an occiput posterior position I made traction on the head while still in the posterior position. After a pull of 35 kilograms there was absolutely no advance of the head. How much greater traction would have been necessary was merely a matter of speculation but it did not seem wise to use more force. The head was then rotated by forceps to an anterior position and delivery was accomplished readily with less than 10 kilograms of traction.

The procedure used to rotate the head is the one which I have always called the modified Seanzoni maneuver (with special emphasis on the "modified"). This procedure is used successfully by all the obstetricians who trained in the Cleveland Maternity Hospital and who are limiting their work to obstetrics and gynecology. We consider it one of the most valuable and most uniformly successful procedures in obstetric practice. Inasmuch as adherence to all steps in the technique of this maneuver is most important, a summary of these is listed here. Granting that the requisites for forceps delivery previously described are present, a double application is made as follows: (1) In the first application the forceps are equally applied over the sides of the head but, of course, are

reversed, grasping the head as if it were in an anterior position. (2) Elevate the handles of the forceps toward the patient's groin. (3) Rotate the head without traction by causing the handles of the forceps to describe a large circle. At the completion of the rotation the handles point almost directly to the floor. To make this possible the buttocks of the patient should be brought slightly over the edge of the table. (4) Rotate to the median line. (5) Moderate traction at this point will fix the head in its new position. (6) Remove the forceps and re-apply them, always inserting the posterior blade first and making a true cephalic application. (7) The rest of the delivery is the same as that in any case of a normal anterior position. A more explanatory description of this maneuver is given in a number of articles in journals. In the second volume of *Obstetrics and Gynecology* by Dr. Carl Henry Davis there is an accurate description of our technique. This should not be confused with various descriptions of the original Scanzoni procedure as has so often been the case. For example, the head is rotated in the pelvic plane in which it lies without traction. There is no spiral combination of turning and pulling which was damaging to the vaginal wall. Let me emphasize the importance of the cephalic application in all cases. The best test of the accuracy of a cephalic application is the relationship of the blades to the lambdoid sutures. They should be equidistant from and parallel with each other. With this application the tips of the blades point toward the child's chin and do not encroach upon the neck with the possibility of pressing upon the umbilical cord, if it happens to be around the neck. They are equally applied to the sides of the head and thus being unlikely to slip make an ideal grasp for both rotation of the head and traction. In cases of transverse arrest it is also possible and advisable to make a cephalic application and to rotate the head to an anterior position. This may be performed by either a single application of the forceps or a double application similar to the maneuver used in the cases of posterior position. I have found the latter procedure to be easier in some cases. Usually transverse arrest is the result of an unsuccessful attempt at spontaneous rotation of a primary posterior position.

Although the pelvic application is described at length in some textbooks I see little place for it. When used, the forceps always grasp the head in a greatly varying but always abnormal manner with unnecessary separation of the blades and with a tendency to slip and therefore a greater chance of damage to the fetal head and the pelvic wall. It is the kind of application which one would make if he did not know the exact position of the head. I do not believe that a physician should apply forceps and make traction without determining the position. Ordinarily it is not necessary to feel an ear to determine the position. The sutures and fontanelles will give sufficient evidence in most cases. However, if there is doubt an ear should be felt.

As to the type of forceps to be used, the old saying that this is not as important as the man behind them is very true. There are, however, in my opinion two general types of forceps, each of which has its advantages, the solid-blade forceps and those with fenestrated blades. The former is better suited for making a good application and for purposes of rotation, while the fenestrated blades



are somewhat better for traction especially when the case is more difficult than the average. We use axis traction handles in all cases, not that this is a means of using greater force but because the greater accuracy of the direction of the pull means that less force will be necessary. With the same idea of using as little force as possible great benefit will come from combining the traction with the uterine contractions as far as possible. If, due to inertia, possibly the result of too deep anesthesia, the contractions are not good enough, moderate pressure from above may sufficiently supplement them. I have always been opposed to the use of pituitary preparations before the birth of the child but have occasionally made one exception to this rule, as follows. If a little more than the ordinary traction is necessary and there are not good uterine contractions, with the head in the anterior position and with the forceps in place with a good cephalic application, a small dose of Pitocin, say 3 minims, may safely be given and traction made simultaneously with the thus stimulated uterine contractions. Taking advantage of the *vis a tergo* will undoubtedly mean a reduction of at least 50 per cent of the necessary traction. In conclusion, the three procedures which have been directly responsible for many of the unfortunate results in the use of forceps and which should be avoided are high forceps, extraction against an insufficiently dilated cervix, and delivery of a head in the occipitoposterior position without rotating it.

In the use of forceps on the aftercoming head the same general principles which have been outlined for the presenting head apply. Thus it is wise to limit the application to the head in the pelvic cavity. If the head is at the inlet it may be brought into the pelvis much more safely by manual manipulation than by forceps. If there is difficulty in delivering the head through the lower part of the pelvis and the outlet, forceps will harm the baby less than the Mauriceau maneuver which has been the cause of brachial paralysis in some cases. Personally I seldom use forceps on the aftercoming head simply because it has not seemed necessary when there has been sufficient manual dilatation and episiotomy.

It is quite important to discuss the practice of using prophylactic forceps, namely, low forceps usually combined with episiotomy. In our experience this procedure is not harmful to the baby if the precautions outlined here are taken. It is not considered an operation merely for shortening labor but as a means of preventing the occurrence of complications which might endanger the life of the child. Examples of these are pressure on the umbilical cord causing a marked slowing of the fetal heart, beginning partial separation of the placenta or fetal distress due to too long and continuous pressure as shown by an increase in the fetal heart rate. Of course, these are definite indications for the use of forceps even if there is a difference of opinion as to the somewhat routine use of prophylactic forceps which has been our custom. We believe that we are justified in anticipating the possible occurrence of such complications even though they are infrequent. The results of our long experience with this procedure definitely confirm our belief that the welfare of both mother and child are safeguarded. I cannot approve of the practice of allowing a patient to go

on for many hours in the second stage of labor and even to continue in labor for several hours when the head may be seen at the vulva, a practice which is taught in some clinics today. We know that if this delay is due to occipitoposterior position, as is commonly the case, this abnormality may be readily corrected with better results than if the patient continues in labor with what is really wasted effort.

### Summary

The requisites and indications for the use of forceps may be summed up as follows.

1. Adequate measurements
2. Fetal head in the pelvic cavity eliminating the high forceps operation
3. Complete dilatation, usually spontaneous, in emergency, artificial
4. Normal anterior position before traction, posterior and transverse positions corrected
5. Axis traction
6. Dependence, as far as possible, on assistance from uterine contractions
7. Elimination of resistance of the pelvic floor, including episiotomy if this seems advisable
8. Use of as little traction force as possible

### Conclusions

Finally, the chief aim is to accomplish delivery by the least possible force, by eliminating factors which could be obstacles to the advance of the head as already outlined. In this light, forceps may be considered instruments for assistance of birth rather than of extraction per se. Their use need not be harmful but on the other hand may be beneficial to the child as well as to the mother.

## DELIVERY OF PATIENTS WITH PELVIC CONTRACTION

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**W**HAT is a contracted pelvis? Williams<sup>1</sup> defined it in the first edition of his text as follows: "We consider a pelvis contracted when it is shortened to such an extent in one or more of its diameters as to affect materially the mechanism of labour, but without necessarily retarding the birth of the child." Greenhill<sup>2</sup> says essentially the same thing: "... clinically every pelvis should be so designated when it is certain that the anomaly has produced a disturbing effect on the parturient function."

That distortion and shortening of certain dimensions of the bony pelvis could affect the course of labor, produce a dystocia making vaginal birth of a living child impossible, or totally prevent vaginal birth of a term-sized infant by embryotomy, has been recognized for centuries. On the other hand, efforts to arrive at precise definition of pelvic contraction by assigning numerical criteria are relatively recent. Thus, it was not until 1861 that Litzmann<sup>3</sup> offered the first numerical criteria for the bony pelvic inlet of the border line between normality and contraction. Williams<sup>4</sup> offered such criteria for the outlet in 1909. The midplane received no attention until 1936, when Hanson<sup>5</sup> published measurements obtained with a specially devised instrument of the transverse diameter of 3,941 women. In the meantime, however, radiographic mensuration was developed to the point where it was possible to get accurate measurement of any two bony prominences recognizable on x-ray film.

Obviously we are interested in the *internal* diameters of the various pelvic planes. Although it is possible to measure most of them manually, the transverse diameter of the inlet defies manual mensuration in the living woman. It is only by radiographic pelvimetry that it can be measured. Many and ingenious are the instruments which have been devised to measure various pelvic diameters. Because some of them were highly complicated, obstetricians have depended for years upon external measurements of the bony pelvis to give a clue as to the size of the internal diameters. Obviously it takes but little reflection to realize that we cannot gain a true idea of *internal* size from external measurements any more than we can ascertain the dimensions of a room by measuring the external dimensions of the building. Fundamentally we are not interested in the *means* by which the internal measurements of the pelvic planes are secured, despite the fact that a great deal of controversy has existed in the past on precisely this point. For the purposes of this paper we assume that any radiographic method correcting

for the divergence of the roentgen rays will measure the pelvis with an accuracy far superior to any clinical need. It is thus absurd to be concerned practically with the method of mensuration. Far more important than *method* is *interpretation* of the measurements after they are made.

The incidence of pelvic contraction is closely allied with etiology. There are, of course, many esoteric types of contraction, depending mainly upon bony congenital anomaly. Chief among these are: assimilation types, those with absence or imperfect development of the alae of the vertebral bodies of the sacrum, and split pelvis. These types are so rare that we seldom encounter them.

We are much more concerned with the ultimate effect of rickets on the bony pelvis. As a normal young girl first sits and then stands, tremendous forces are brought to bear upon the bony pelvis which alters itself accordingly. If, in addition, and particularly at the time when the child first begins to sit and walk, there is the added factor of rickets, certain recognizable anomalies and modifications develop. Frequently stigmas of rickets may be observed in the bony pelvis when it is impossible to find them elsewhere. Actually these stigmas should be taught by the internist and should not be the sole property of the obstetrician. Since most pelvic anomalies, except the esoteric types mentioned, depend upon softening of the bones during developmental periods, it is obvious that more pelvic distortion will be seen among the socially underprivileged than among the privileged. It is, also, completely unrealistic to contrast the incidence of pelvic contraction today with the incidence of pelvic contraction years ago when the prophylaxis of rickets was poorly understood. Finally, criteria of pelvic contraction vary. For all these reasons, we will not attempt to offer figures on incidence of bony pelvic contraction, but will merely report those at Parkland Hospital where most of our clientele is Negro and indigent. We found 946 contracted pelvises among a total of 13,087 patients, or an incidence of 7.2 per cent. For the purposes of record keeping we code a pelvis as contracted when the inlet or the midplane presents an area of 85 per cent, or less, than average.

Our interest in pelvic contraction was stimulated by the case of a 22-year-old primigravida who was delivered vaginally by craniotomy June 17, 1945.

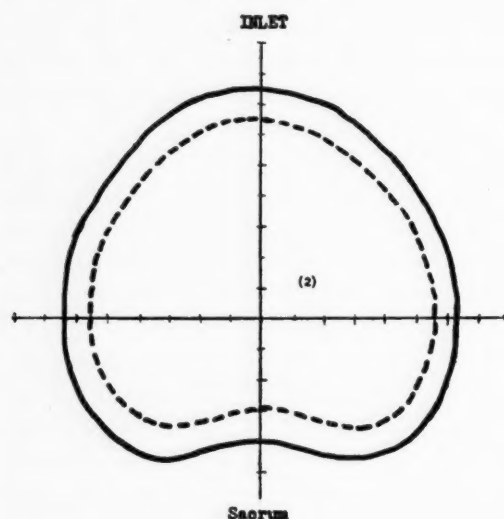
Manually the inlet and outlet measurements were within normal limits as follows:

<i>Inlet.</i> —	
Interspinous	25.0 cm.
Intercristal	26.5 cm.
External conjugate	19.0 cm.
Diagonal conjugate	11.7 cm.
<i>Outlet.</i> —	
Transverse	8.5 cm.
Posterior sagittal	8.0 cm.
Anteroposterior	11.5 cm.

We recognized no problem and the patient was allowed to enter the hospital in labor. The cervix was effaced, 4 cm. dilated, the head was fixed at the inlet in left occipitotransverse presentation, and the amniotic sac had ruptured. During the next eight and one-half hours the vertex descended slightly below the spines and the cervix dilated to 8 cm. *Ten hours later despite hard uterine contractions the situation was unchanged.* Twenty and one-half hours after admission the blood pressure dropped to 80/60, the fetal heart tones became inaudible, and fetal movements ceased. Shock was combated,

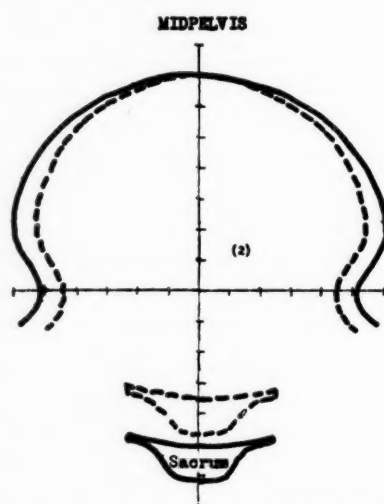


craniotomy was performed, and the bladder inadvertently perforated. The assembled fetal parts weighed 3,587 grams. After the event we measured this patient's pelvis radiographically and discovered that the inlet capacity was 74.5 per cent and the midplane capacity 73.8 (Figs. 1A and 1B). Obviously she should have had elective abdominal section. In passing it should be reported that the vesicovaginal fistula was subsequently successfully repaired.



	Normal	Patient
Anteroposterior	11.6	9.5
Transverse	12.5	11.4
AP x transverse	145.0	108.1
Percentage	100.0	74.5

Fig. 1A.



	Normal	Patient
Anteroposterior	12.1	10.5
Transverse	10.3	8.8
AP x transverse	124.6	92.3
Percentage average capacity	100.0	73.8
Posterior sagittal	5.2	3.5

Fig. 1B.

This case taught us a lesson and inaugurated almost routine radiographic pelvic mensuration.

At the present time we measure radiographically the pelvis of each primigravida and of every multigravida with a history of obstetric difficulty. For those who do not find such routine financially feasible we have developed a series of "criteria of suspicion," and believe that it is virtually mandatory to measure the pelvis radiographically when any one of the following is present.

#### CRITERIA OF SUSPICION

##### A. History.—

1. Difficult labor
2. Midforceps
3. Unexplained stillbirth

##### B. Palpation.—

1. Inlet
  - a. Ability to touch sacral promontory vaginally
  - b. Overriding, head over symphysis
  - c. Failed impression maneuver
2. Midplane
  - a. Prominent ischial spines
  - b. Sacral deformity
3. Outlet
  - a. Fist will not go between tuberosities

##### C. Nonengagement (Primigravida at term)

We have now not only abandoned manual mensuration but no longer teach it to the medical students.

Our efforts at evaluation of the capacity of the bony pelvis have been detailed elsewhere.<sup>6-9</sup> At first we recognized and assayed the capacities of three pelvic planes: inlet, midplane, and outlet. Later we abandoned the estimation of outlet capacity. This was after we discovered that the transverse diameter of the outlet was less than the transverse diameter of the midplane in only two patients of the series. Now we believe that a narrowed outlet represents no more than reflection of a transverse midplane contraction. To put it differently, we feel that if the transverse diameter of the midplane is normal, it is virtually impossible for the transverse diameter of the outlet to be significantly contracted.

The average pelvic measurements of a series of 1,718 patients are included in Table I. We do not calculate the *actual* area of the inlet or of the midplane. To do so would involve a planimeter and is unnecessary since we *compare* a given patient with established averages. The anteroposterior is multiplied by the transverse to give us a factor, or index. From Table I it will be seen that in the first series this index was 145 sq. cm. for the inlet and 125 for the midplane. Since these represent round, and easily remembered numbers, we accepted them. In a given patient the index of the inlet and of the midplane is calculated. Each of these indices is then compared with the average above. In other words the inlet of a given patient will have a certain percentage of 145 sq. cm. Thus, if the product of her inlet anteroposterior and transverse diameters is 159.7 she will have 110 per cent of inlet capacity. If the product of these diameters is 123.2 sq. cm. she will have 85 per cent of inlet capacity. In a similar manner it is possible to calculate the percentage capacity of the midplane.

TABLE I. AVERAGE PELVIC DIAMETERS RADIOGRAPHICALLY MEASURED (CENTIMETERS)

	ACCEPTED STANDARDS	SERIES I 935 PATIENTS	SERIES II 1,718 PATIENTS (INCLUDING SERIES I)	
			AVERAGE	MEDIAN
<i>Inlet.</i> —				
Anteroposterior	11.5	11.6	11.8	11.9
Transverse	13.0	12.5	12.4	12.7
AP × Trans.		145.0	146.3	151.1
<i>Midplane.</i> —				
Anteroposterior	11.5	12.1	11.9	12.3
Transverse	10.5	10.3	10.6	10.8
AP × Trans.		124.9	126.1	132.8

Table II shows the outcome of labor when inlet capacities progressively are reduced below 90 per cent, and Table III shows the same thing for the midplane. It is obvious from these tables that somewhere between 90 and 85 per cent of average capacities there is a "break-away" point. When pelvic capacities are reduced below this point, the difficulties and dangers of vaginal delivery are progressively increased.

TABLE II. INLET: COMPARISON OF CAPACITIES

	NUMBER OF PATIENTS	CESAREAN SECTION		MIDFORCEPS		NECESSARY OPERATIONS		FETAL DEATH	
		NUM- BER	PER- CENT- AGE	NUM- BER	PER- CENT- AGE	NUM- BER	PER- CENT- AGE	NUM- BER	PER- CENT- AGE
90% or more	1,314	15	1.1	41	3.1	6	0.5	30	2.3
89% or less	301	19	6.3	20	6.7	3	1.0	13	4.3
84% or less	131	14	10.7	10	7.6	2	1.5	6	4.6
79% or less	57	10	17.5	5	8.8	1	1.8	3	5.3

TABLE III. MIDPLANE: COMPARISON OF CAPACITIES

	NUMBER OF PATIENTS	CESAREAN SECTION		MIDFORCEPS		NECESSARY OPERATIONS		FETAL DEATH	
		NUM- BER	PER- CENT- AGE	NUM- BER	PER- CENT- AGE	NUM- BER	PER- CENT- AGE	NUM- BER	PER- CENT- AGE
90% or more	1,274	15	1.2	35	2.7	6	0.5	35	2.6
89% or less	341	19	5.7	26	7.6	3	0.9	10	2.9
84% or less	146	17	11.6	11	7.5	3	2.1	4	2.7
79% or less	67	13	19.4	4	6.0	1	1.5	2	2.9

There are five components of cephalopelvic disproportion.

1. Size and shape of the bony pelvis
2. Size of the fetal head
3. Force exerted by the uterus
4. Moldability of the head
5. Presentation and position

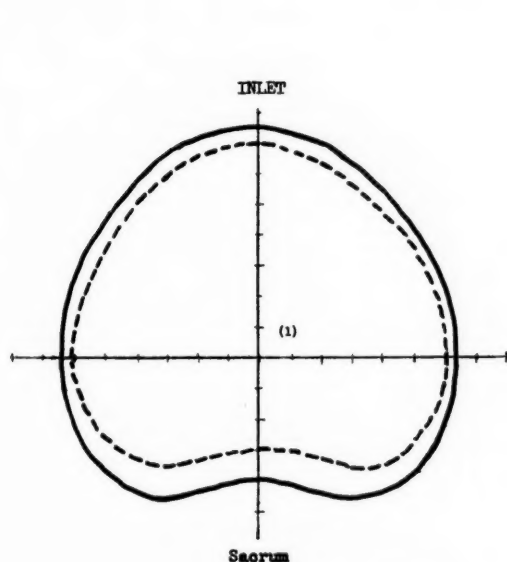
Of them, only one is susceptible to accurate measurement. Many and varied have been the attempts to measure the size of the fetal head antenatally. From the clinical standpoint, however, estimation of fetal head size in three groups suffices: large, medium, and small. We believe this can be done with sufficient accuracy for any clinical need by the third Leopold maneuver, the "C" grip.

No one of the remaining three components of cephalopelvic disproportion can possibly be ascertained until the patient is actually in labor. The absurdity, therefore, in patients with borderline pelvises of attempting to prognosticate the likelihood of vaginal birth before any one of these three components is known, is obvious. Moreover, these three antenatally imponderable components make it unlikely that cephalopelvic disproportion can ever be reduced to a mathematical formula.

Of the components of cephalopelvic disproportion, obviously the size of the bony pelvis is the most important. When our radiographic studies on the pelvis were started nine years ago, we believed the second most important component was the size of the fetal head. Today, we are inclined to believe that the force of uterine contraction is more important than any other component except pelvic size. For example, given two women with the same type and degree of contraction and with children of the same size, the one

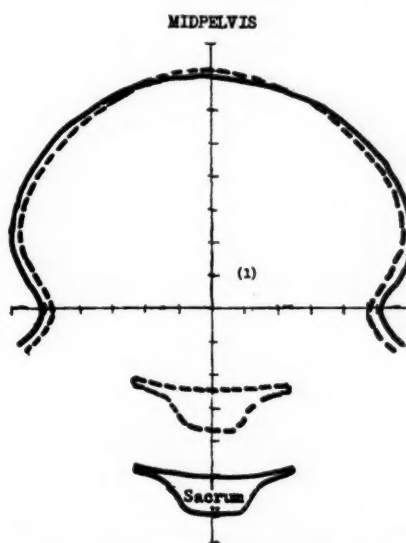
with better than average force and the other with less than average force, it is entirely likely that the first will give birth to her baby spontaneously while the second may not. This brings us immediately to the question of what constitutes a test of labor.

Every physician who has to do extensively with childbirth knows that no woman has experienced an adequate trial until she has been in labor two hours in the second stage without advance, with the cervix fully dilated and retracted behind the presenting part and the membranes ruptured. On the other hand, such a test is neither feasible nor safe in every instance, and seldom is desirable. Thus, we compromise and tend to allow a patient with cephalopelvic disproportion to labor a certain prearranged number of hours. This is not really a test of the pelvis, but is a *test of the forces of labor*.



	Normal	Patient
Anteroposterior	11.6	10.1
Transverse	12.5	12.2
AP x transverse	145.0	123.2
Percentage	100.0	84.9

Fig. 2A.



	Normal	Patient
Anteroposterior	12.1	9.7
Transverse	10.3	9.6
AP x transverse	124.6	93.3
Percentage average capacity	100.0	63.8
Posterior sagittal	5.2	2.6

Fig. 2B.

### Clinical Applications

During the course of our studies on the delivery of women with pelvic contraction, certain typical situations were recognized. It is obviously impossible in a paper of this length to discuss each of these in detail, but it is possible to give examples of the situations which often arise.

#### *Transverse Adequate.*—

Of the two pelvic diameters, the anteroposterior and the transverse, shortening of the former is more innocuous than shortening of the latter. In other words, the platypelloid pelvis is less likely to hinder or modify labor



than the anthropoid pelvis. To put it still differently, a patient frequently will have a spontaneous outcome of labor if the transverse diameters of the pelvis are adequate.

Figs. 2A and 2B represent the pelvis of a 15-year-old gravida i, para 0, who weighed 123 pounds and was 5 feet, 1 inch tall. After 2½ hours of active labor the cervix was effaced and 3 cm. dilated. The head was fixed in the inlet, with the vertex well above the ischial spines and the membranes were already ruptured. In reviewing the graphs of this pelvis, it is obvious that it is small. The sacrum was straight and vertical with a forward angulation of the last two segments. Passage was deemed possible for a small baby if the head lay in a favorable position, namely transverse. Labor was allowed to continue in view of the nearly adequate transverse diameters and because of the mother's youth. The first stage lasted 23 hours, the second 1 hour, and the child weighed 2,912 grams. This pelvis was small and the midplane capacity but 64 per cent of average. Nevertheless, delivery was possible and did occur and demonstrated that arrest of labor at any level is unlikely if the transverse diameters are adequate.

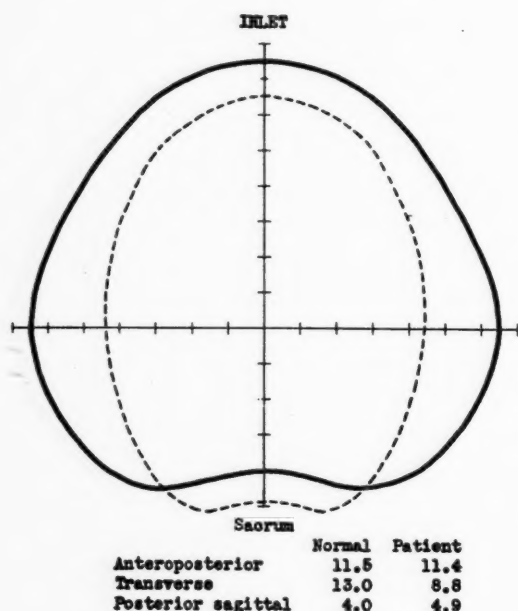


Fig. 3A.

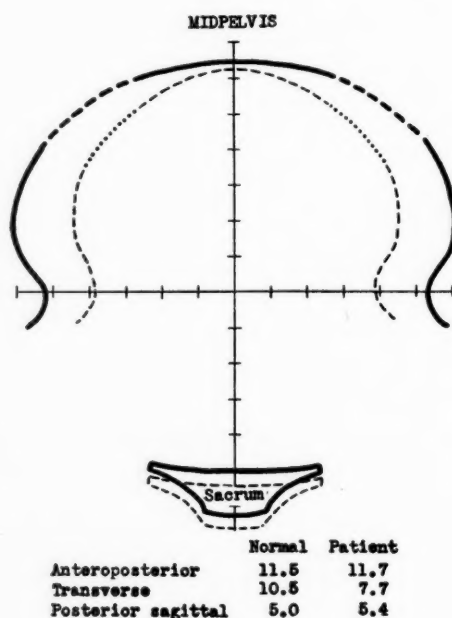


Fig. 3B.

This patient gave birth to her baby spontaneously in 1946. Today, with more experience, we would feel that this was not a good gamble despite the favorable outcome and would submit a similar patient to elective abdominal section.

#### *Transverse Inadequate.*—

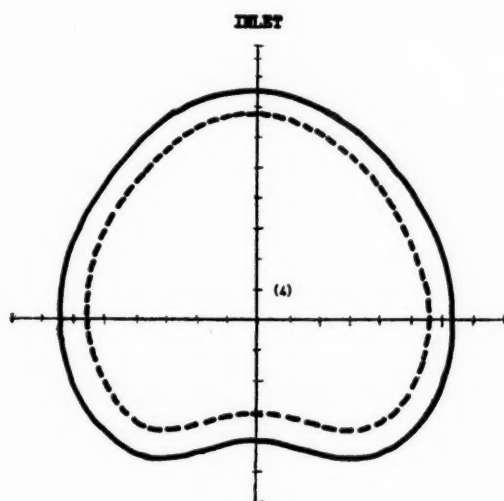
During the years that we were intensively studying pelvises and allowing almost every patient with contracted pelvis to have extensive labor before interference, the patient whose pelvis is illustrated in Figs. 3A and 3B appeared.

Because of the anthropoid type of pelvis with a transverse inlet diameter of 8.8 and midplane diameter of 7.7 cm., we did not allow her to have any labor at all, but delivered her abdominally, prior to the onset of labor.

*Isolated Inlet Contraction.*—

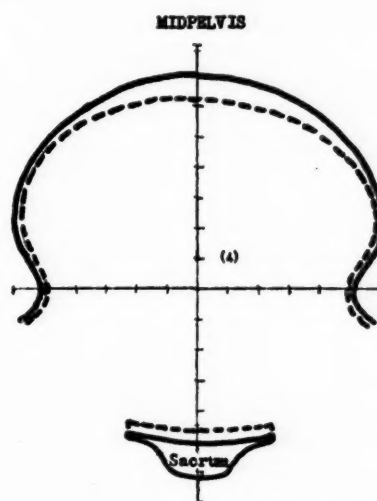
The next patient represents a most favorable type of pelvic deformity, namely the isolated inlet contraction (Figs. 4A and 4B).

This was a primigravida, aged 17 years, who weighed 121 pounds and was 4 feet, 8 inches tall. She was admitted in labor with the head floating, the cervix effaced and 1 cm. dilated. The bag of waters was intact. Obviously the critical plane is the inlet and any head negotiating it can readily traverse the midplane. *This is the ideal situation for trial of the forces of labor.* During the ensuing 8 hours the head molded through the inlet. After the biparietal diameter passed the superior strait, labor was precipitate with birth of a 2,381 gram infant 30 minutes later.



	Normal	Patient
Anteroposterior	11.6	9.8
Transverse	12.5	11.2
AP x transverse	145.0	109.6
Percentage	100.0	75.6

Fig. 4A.



	Normal	Patient
Anteroposterior	12.1	10.8
Transverse	10.3	10.0
AP x transverse	124.6	108.0
Percentage average capacity	100.0	86.3
Posterior sagittal	5.2	4.6

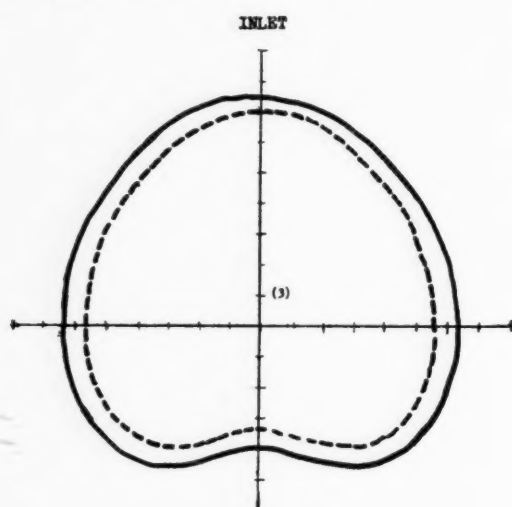
Fig. 4B.

Isolated inlet contraction seldom constitutes a serious problem since it lends itself so readily to the trial of the forces of labor. On the other hand, the reversal of inlet and outlet capacities in this particular instance would constitute a serious problem. By the time the biparietals arrive in the midplane, labor generally is so far advanced that abdominal section becomes increasingly a hazardous gamble.

*Two-Plane Contraction.*—

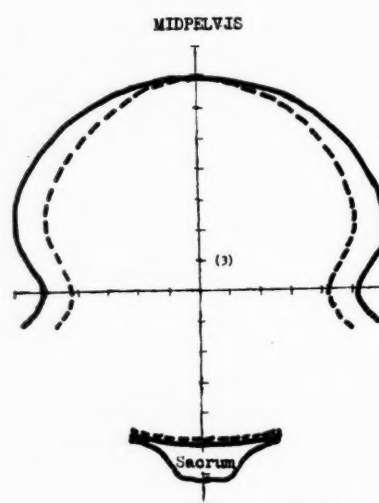
The next patient represents a two-plane contraction. In our experience moderate contraction of both the inlet and midplane is a more serious situation than a severe contraction of either plane (Figs. 5A and 5B).

This patient was a 17-year-old primigravida who weighed 119 pounds and was 5 feet, 3 inches tall. After 7 hours of active labor with the membranes ruptured, the head was fixed in the inlet in left occipitotransverse presentation. The cervix was effaced and admitted a finger tip. From study of the midplane graph it is obvious that an average-sized infant might pass the midplane with difficulty, provided the occiput were anterior. Therefore, the head would have to rotate at least 90 degrees between inlet and midplane since passage of the head through the latter with the sagittal suture transverse is manifestly impossible. We considered the possibility of cesarean section but decided to allow the patient to labor. After a 21 hour first stage and a 3 hour second stage there was only slight descent with arrest of the head in left occipitotransverse. A midforceps operation was performed and resulted in the birth of a normal 3,545 gram infant. In the puerperium, however, the mother developed severe endometritis and pelvic cellulitis. We knew of the pelvic contraction in this patient sufficiently early in labor to have delivered her abdominally. Today we would do so. On the other hand, this is the type of patient who makes the physician, unaware of the situation, wonder *after the delivery* why the forceps operation was so difficult!



Sacrum		
	Normal	Patient
Anteroposterior	11.6	10.6
Transverse	12.5	11.6
AP x transverse	145.0	121.9
Percentage	100.0	83.8

Fig. 5A.



	Normal	Patient
Anteroposterior	12.1	12.0
Transverse	10.3	8.4
AP x transverse	124.6	101.0
Percentage average capacity	100.0	80.8
Posterior sagittal	5.2	5.1

Fig. 5B.

The development of severe pelvic cellulitis is of considerable significance because it is obvious that whenever maternal soft tissues are unduly traumatized between the bony pelvis and the head, those tissues are rendered more susceptible to subsequent infection. From the clinical standpoint pelvic cellulitis occurs frequently after vaginal delivery in patients with moderately contracted pelvis. To sum up, a two-plane contraction, especially when it is necessary for the sagittal suture to change axis through 90 degrees is much worse than a single plane contraction of considerable severity.

#### *Presentation and Position.—*

The next patient represents the effect of presentation and position upon the outcome of labor.

She was 22 years old, a gravida ii, para 0, who weighed 122 pounds and was 5 feet, 2 inches tall. The vertex was fixed in the inlet in right occipitoposterior position after 12 hours of active labor. The cervix was completely effaced and 3 cm. dilated and the bag of waters was intact. Figs. 6A and 6B graphically portray the inlet and midplane of this patient. The anthropoid inlet suggests that engagement would occur best as an occiput directly or obliquely posterior. In fact it did occur as a right occipitoposterior. On the other hand, in order to traverse the midplane, a 180 degree rotation to occiput anterior would be desirable but extremely unlikely. We felt, therefore, that in all probability the head would engage as an occiput posterior and come to an arrest at, or below, the midpelvis with the occiput obliquely posterior. Furthermore, we felt that if events did transpire as we anticipated, forceps delivery would best be consummated with the occiput deliberately turned into the hollow of the sacrum, rather than to attempt anterior rotation. The vertex arrested 2 fingerbreadths below the spines with the occiput directly posterior, after 14 hours of first stage. There was no progress during the first 2 hours of the second stage. Therefore, forceps extraction was performed and resulted successfully in the birth of a 2,978 gram infant. The operator delivered the child with the occiput directly posterior and was pleased with the relative ease of accomplishment.

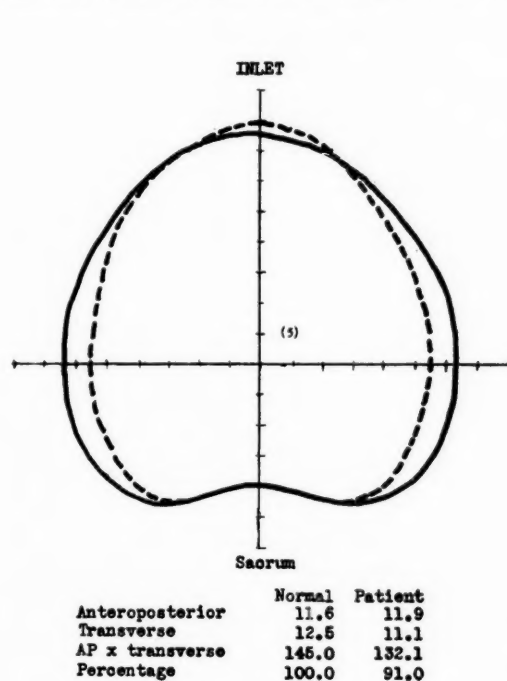


Fig. 6A.

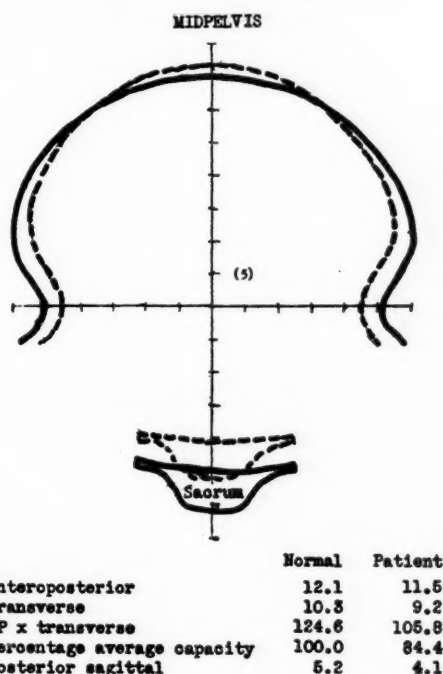


Fig. 6B.

Although presentation and position do not often enter so dramatically into borderline pelvic contraction, they did in this particular instance. Had the vertex by chance engaged as an occiput anterior, the labor would probably have been seriously complicated.

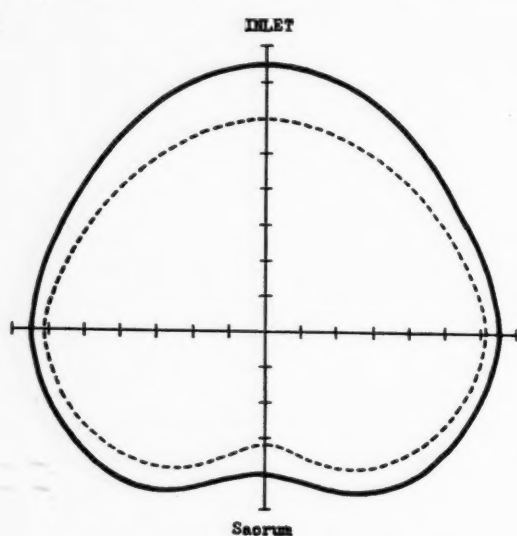
#### *Prediction of Modifications of Labor Mechanisms.—*

By virtue of graphic portrayal of pelvic shape, we saw in the preceding case that sometimes it is possible to make a shrewd guess concerning the course of labor. This is even more obvious in the next patient with a platypelloid pelvis (Figs. 7A and 7B).



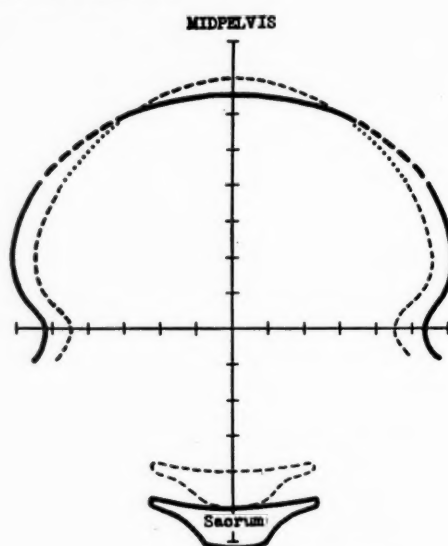
It is obvious from the shape of the pelvis that the head must descend to the pelvic floor before anterior rotation can occur. It is also obvious that with a two-plane contraction, both below 80 per cent, today we would submit this woman to elective cesarean section. Since the child, by abdominal palpation, was average or better in size we predicted a transverse midpelvic arrest. The total length of labor was 32 hours. As predicted, the head engaged transversely and was arrested in the midplane without rotating. A Kjelland forceps operation was performed after a  $3\frac{1}{2}$  hour second stage, and as predicted it was impossible to affect rotation until descent to the pelvic floor had been achieved. The child weighed 3,692 grams.

This represents a great advantage of the graphic area method of pelvic evaluation, namely, the ability on occasion to be able to predict the modifications of the labor mechanisms imposed by the pelvic distortion.



	Normal	Patient
Anteroposterior	11.5	9.2
Transverse	13.0	12.3
Posterior sagittal	4.0	3.2

Fig. 7A.



	Normal	Patient
Anteroposterior	11.5	11.0
Transverse	10.5	9.0
Posterior sagittal	5.0	4.0

Fig. 7B.

#### *Primary Uterine Inertia.—*

In two other situations the advantages of foreknowledge concerning the pelvis are important, namely, primary uterine inertia and breech presentation. With primary uterine inertia it is highly desirable to know that the pelvis is normal, before any stimulatory treatment is instituted. When certain knowledge is available that inlet and midplane capacities are 100 per cent or better, treatment of a primary uterine inertia may be conducted without the gnawing doubt of a coexisting cephalopelvic disproportion.

#### *Breech.—*

When the head is aftercoming, it is highly desirable to know the pelvis is normal. We can afford to allow a patient with the child presenting by the vertex and with a minor pelvic contraction to mold the head through the

pelvis. Conversely, to allow a patient with a known pelvic contraction to labor with a breech is undesirable. In the latter instance there would be no time for the aftercoming head to mold, and the head might well be compressed beyond endurance of the falx and tentorium.

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## **EIGHT THOUSAND PARTURIENTS EVALUATE DRUGS, TECHNIQUES, AND DOCTORS DURING LABOR AND DELIVERY**

### **A Qualitative and Quantitative Assay of Obstetrical Amnesia, Analgesia, Anesthesia, and Psychological Lobotomy During Childbirth**

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**D**URING the decade past, progress in the understanding and utilization of the principles of obstetric analgesia and anesthesia during childbirth has exceeded the accomplishments of the previous century so dramatically and effectively introduced by the lifework of Sir James Y. Simpson. More than eight hundred scientific articles and a half dozen texts in many languages have presented physicians' evaluation of multiple presently used methods in the control of obstetric pain. This paper is the first evaluation of obstetrical amnesia, analgesia, and anesthesia and psychorelaxation methods by a statistically significant group of parturients who themselves experienced the effects of these drugs or the lack of them during childbirth.

The study was a small part of a total evaluation of all presently used methods in the control of obstetric pain conducted in the Johns Hopkins and Sinai Hospitals in Baltimore during 1948-1951 as a planned project supported by the staffs of the two hospitals in cooperation with the United States Public Health Service and nine of the major pharmaceutical companies† in America. Other aspects of the study relating to fetal salvage and wastage and maternal mortality and morbidity have been completed and will be published in a separate monograph.

The IBM punch cards were used throughout the study in the tabulating of eighty columns of medical, obstetrical, anesthesiological, and pharmacological data which were recorded frequently and regularly during labor and delivery and in postdelivery follow-up of all of the patients by a specially trained team of special anesthesia assistant obstetrical nurses who were available 24 hours daily for the three years of the study. The data were first recorded on the patient's charts and on the same day transcribed to individual code sheets using a numerical system identical with the IBM cards. The final recording was made on the IBM cards with one for each mother and one for each baby by clerks in the department of obstetrical statistics of the Johns Hopkins Hospital. The organization of the data into tables and charts was performed by the Section on Statistics in the Division of Public Health Methods in the United States Public Health Service under the direction of Dr. S. D. Collins.

\*Senior Surgeon, United States Public Health Service.

†Made possible by grants to the obstetrical anesthesia research program of the Johns Hopkins University and Hospital from Abbott Laboratories, Astra Pharmaceutical Products, Inc., Ciba Pharmaceutical Products, Inc., Eli Lilly and Company, Merck & Co., Inc., Parke, Davis & Company, Sharpe & Dohme, Inc., E. R. Squibb & Sons, Winthrop-Stearns, Inc., and Becton, Dickinson and Company.

There were 9,347 mothers in this study. In order that certain heterogeneous variables could be removed, those mothers who delivered multiple births, infants who died in utero before labor and analgesia, and infants with congenital abnormalities incompatible with life and those delivered by cesarean section were excluded. This left 7,704 mothers with live single fetuses in utero at the onset of analgesia as can be seen by summary Tables I, II, and III. There was a widespread distribution among all categories of primiparas and multiparas, white and nonwhite, private and ward patients. Likewise, as can be seen in Figs. 1 and 2 and Table III, there were statistically significant groups managed with each of the various methods of obstetrical analgesia and anesthesia.

TABLE I. SUMMARY. TOTAL NUMBERS ONLY (NO EXCLUSIONS)

	BOTH HOSPITALS	HOPKINS	SINAI
<i>Total infants</i>	9,472	5,856	3,616
Live births	9,337	5,757	3,580
Neonatal deaths	130	103	27
Congenital malformations	32	23	9
Stillbirths	135	99	36
Infants who died before onset of labor and analgesia	110	83	27
Congenital malformations	3	1	2
Multiple births	249	179	70
First births	124	89	35
Second and third births	125	90	35
Deaths among multiple births	8	6	2
Stillbirths among multiple births	11	10	1
Premature infants	993	721	272
Private patients	271	103	168
White	264	96	168
Nonwhite	7	7	-
Ward patients	722	618	104
White	257	153	104
Nonwhite	465	465	-
Cesarean sections	105	83	22
Twins*	126	98	28
<i>Total mothers</i>	9,347	5,766	3,581
Ward mothers	5,354	4,233	1,121
White	2,497	1,377	1,120
Nonwhite	2,857	2,856	1
Private	3,993	1,533	2,460
White	3,928	1,472	2,456
Nonwhite	65	61	4
Primiparas	2,918	1,701	1,217
White	2,062	848	1,214
Nonwhite	856	853	3
Multiparas	6,429	4,065	2,364
White	4,363	2,001	2,362
Nonwhite	2,066	2,064	2
Mothers with breech	315	195	120
Mothers with cesarean sections	407	315	92
Mothers with diabetes	29	23	6
Mothers with heart disease	202	144	58
Mothers with hemorrhagic conditions	379	293	86
Mothers with obesity	200	130	70
Mothers with toxemia	997	755	243
Mothers with tuberculosis	159	134	25
Maternal deaths	6	6	-

\*Twins counted as premature only when both twins weighed less than 2,500 grams.



TABLE II. PERCENTAGE OF MOTHERS WITH SPECIFIED PSYCHOLOGICAL EVALUATIONS ACCORDING TO METHODS OF ADMINISTERING DRUGS (HOPKINS AND SINAI)

METHODS	PERCENTAGE			NUMBER*			
	SATIS-FACTORY	PAR-TIALLY SATIS-FACTORY	UNSATIS-FACTORY	MOTH-ERS' KNOWN EVAL.	SATIS-FACTORY	PAR-TIALLY SATIS-FACTORY	UNSATIS-FACTORY
<i>All Mothers.—</i>							
Total mothers	81.7	10.2	8.1	7,704	6,297	785	622
No anesthesia	73.2	11.4	15.4	643	471	73	99
No anes. or anal.	69.3	10.4	20.3	374	259	39	76
Intravenous	79.9	11.8	8.3	558	446	66	46
Inhalation	77.4	12.4	10.2	2,153	1,666	267	220
Caudal†	86.1	7.3	6.6	1,529	1,317	111	101
Spinal	87.2	8.5	4.3	2,388	2,083	202	103
Local	69.5	17.8	12.7	197	137	35	25
Combination of methods	75.0	13.1	11.9	236	177	31	28
<i>Primiparas.—</i>							
Total mothers	85.5	8.2	6.3	2,483	2,122	204	157
No anesthesia	76.3	13.5	10.2	59	45	8	6
No anes. or anal.	61.5	23.1	15.4	26	16	6	4
Intravenous	80.1	11.8	8.1	186	149	22	15
Inhalation	79.9	10.9	9.2	523	418	57	48
Caudal†	89.4	6.0	4.6	587	525	35	27
Spinal	89.3	6.6	4.1	974	870	64	40
Local	72.5	14.5	13.9	69	50	10	9
Combination of methods	76.5	9.4	14.1	85	65	8	12
<i>Multiparas.—</i>							
Total mothers	80.0	11.1	8.9	5,221	4,175	581	465
No anesthesia	73.0	11.1	15.9	584	426	65	93
No anes. or anal.	69.8	9.5	20.7	348	243	33	72
Intravenous	79.9	11.8	8.3	372	297	44	31
Inhalation	76.6	12.9	10.5	1,630	1,248	210	172
Caudal†	84.4	7.9	7.7	942	792	76	74
Spinal	85.8	9.8	4.4	1,414	1,213	138	63
Local	68.0	19.5	12.5	128	87	25	16
Combination of methods	74.2	15.2	10.6	151	112	23	16

\*Twins, cesarean sections, infants who died before onset of labor and analgesia, and infants with congenital malformations incompatible with life are excluded.

†Caudal includes a few mothers delivered by special conduction and peridural anesthesia.

At the onset of the study, it was determined that parturients in the Hopkins Hospital would be managed with one of the five following group plans considered to embody the standard presently used methods of analgesia and anesthesia:

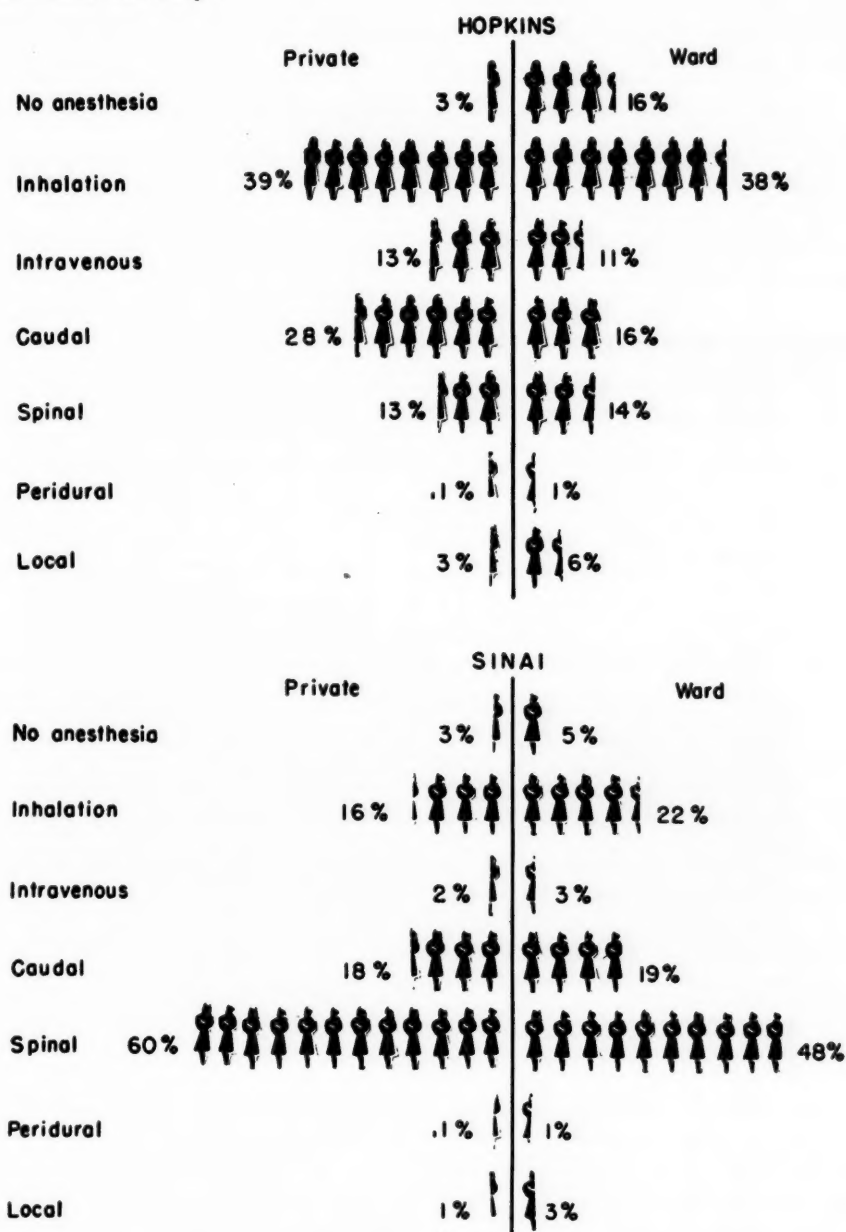
1. Group I. Systemic sedation for labor and general inhalation anesthesia for delivery with agents nitrous oxide, ether, cyclopropane, and trichloroethylene.

2. Group II. Systemic sedation for labor and intravenous barbiturate anesthesia for delivery with agents Pentothal sodium, Surital, Seconal, and Nembutal.

3. Group III. No drugs exceeding 50 mg. Demerol during labor or delivery, but psychoanalgesia established with suggestion, comfortable air-conditioned environment, therapeutic music and interior decorating.

4. Group IV. Systemic sedation for labor with terminal conduction block of spinal, caudal, or local for delivery.

5. Group V. Continuous conduction block without systemic narcosis during labor and delivery.



Each symbol = 5% of mothers with specified method

Fig. 1.

In the Sinai Hospital the staff and directors of the obstetrical department felt that a study of a group of patients receiving no analgesia or anesthesia

should not be done. Consequently, three methods of management were decided upon which coincided entirely with the four groups in the Hopkins Hospital which were conducted with analgesic and anesthetic drugs. The sedation for labor and inhalation with intravenous anesthesia for delivery were combined into a single group designated as Group C. These three methods recorded in Table V are:

1. Group A. Systemic sedation for labor and terminal block with spinal (saddle block) for delivery.
2. Group B. Continuous conduction caudal or peridural analgesia for labor and delivery without systemic narcosis.
3. Group C. Systemic sedation for labor and inhalation or intravenous anesthesia for delivery.

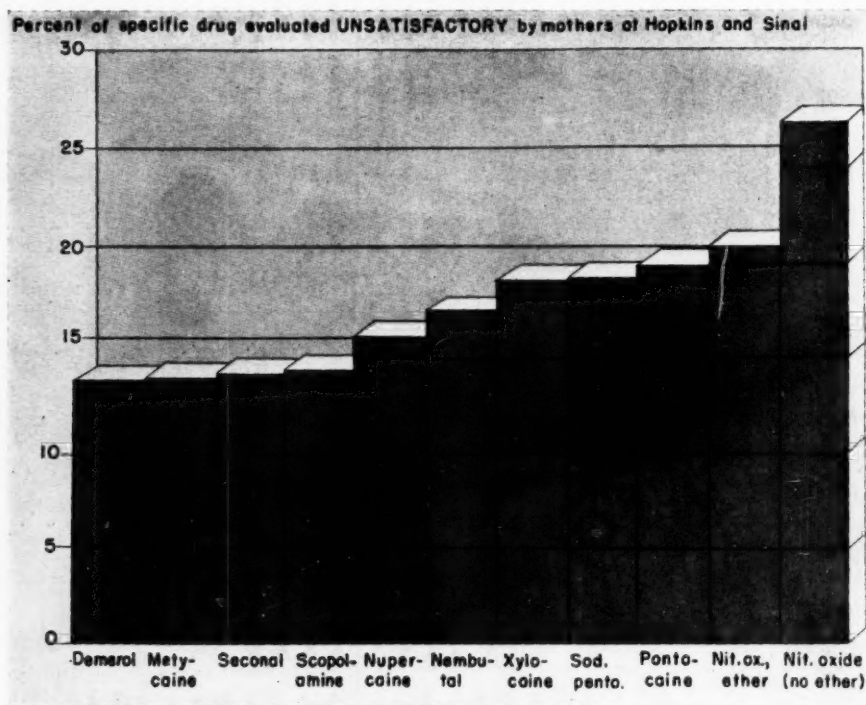


Fig. 2.

### Labor-Room Environment

Comfortable and pleasing environment, while not directly linked with evaluation of drugs and other treatments, has a definite influence upon emotional and psychological reactions. Therefore, the standard type labor rooms in these hospitals, hitherto strictly functional, have emerged as chambers of restful grace. The new "climate" for labor is established in air-conditioned, soundproof rooms where the comparatively harsh finish of old-style hospital rooms has given way to cool pastel tints following established rules of color therapy. Peach, cascade blue, soothing grey, and pinkish glow rooms are equipped with modern indirect lighting fixtures, venetian blinds, and appro-

TABLE III. PERCENTAGE OF MOTHERS WITH SPECIFIED PSYCHOLOGICAL EVALUATIONS FOR EACH METHOD OF ADMINISTERING DRUGS ACCORDING TO HOSPITAL ACCOMMODATIONS (HOPKINS AND SINAI)

METHODS	PERCENTAGE			NUMBER*			
	SATIS- FACTORY	PAR- TIAL- SATIS- FACTORY	UNSATIS- FACTORY	MOTH- ERS' KNOWN EVAL.	SATIS- FACTORY	PAR- TIAL- SATIS- FACTORY	UNSATIS- FACTORY
<i>All Accommodations.—</i>							
Total mothers	81.7	10.2	8.1	7,704	6,297	785	622
No anesthesia	73.2	11.4	15.4	643	471	73	99
No anes. or anal.	69.3	10.4	20.3	374	259	39	76
Intravenous	79.9	11.8	8.3	558	446	66	46
Inhalation	77.4	12.4	10.2	2,153	1,666	267	220
Caudal†	86.1	7.3	6.6	1,529	1,317	111	101
Spinal	87.2	8.5	4.3	2,388	2,083	202	103
Local	69.5	17.8	12.7	197	137	35	25
Combination of methods	75.0	13.1	11.9	236	177	31	28
<i>Private.—</i>							
Total mothers	89.7	6.6	3.7	3,497	3,137	232	128
No anesthesia	93.1	5.9	1.0	101‡	94	6	1
No anes. or anal.	91.7	8.3	—	24‡	22	2	—
Intravenous	85.8	8.2	6.0	183	157	15	11
Inhalation	88.9	8.0	3.1	804	715	64	25
Caudal†	90.6	5.4	4.0	795	720	43	32
Spinal	90.3	6.3	3.4	1,468	1,326	93	49
Local	84.2	10.5	5.3	38	32	4	2
Combination of methods	86.1	6.5	7.4	108	93	7	8
<i>Ward.—</i>							
Total mothers	75.1	13.2	11.7	4,207	3,160	553	494
No anesthesia	69.5	12.4	18.1	542	377	67	98
No anes. or anal.	67.7	10.6	21.7	350	237	37	76
Intravenous	77.1	13.6	9.3	375	289	51	35
Inhalation	70.5	15.0	14.5	1,349	951	203	195
Caudal†	81.3	9.3	9.4	734	597	68	69
Spinal	82.3	11.8	5.9	920	757	109	54
Local	66.0	19.5	14.5	159	105	31	23
Combination of methods	65.6	18.8	15.6	128	84	24	20

\*Twins, cesarean sections, infants who died before labor and analgesia, and infants with congenital malformations incompatible with life are excluded.

†Caudal includes a few mothers delivered by special conduction and peridural anesthesia.

‡These 101 mothers represent only the residue of a much larger number of private patients who required drugs and anesthetics after a few hours' trial of psychoanalgesia in early labor.

priately chosen draperies. Attractive wall mirrors, oil and watercolor paintings of landscapes blend with the wall finish. Therapeutic background music is transmitted by MUZAK into each labor and delivery room on a 24 hour per day optional basis. Individual volume controls permitted patient use of the music to the volume tone desired or eliminated altogether. The same environment was offered to private and service cases and to all races without exception. The patients themselves almost unanimously have appraised music as one of the most invaluable and pleasant remedies for the emotional tension so frequently attending prodromal and active labor and delivery.

#### Method of Determining Psychological Evaluation

Twenty-four hours after delivery the patient was visited for the first time by a secretary trained for interviews who explained the purpose of her visit as a means of assaying the efficiency of analgesics and anesthetics and methods. The



patient was encouraged to designate her pain relief during labor and delivery as "excellent, good, satisfactory, partially satisfactory, or unsatisfactory." The data were then entered on the patient's code sheet and correlated with the evaluations of the physician and obstetrical nurse anesthesia assistant who managed this particular patient. In less than 0.5 per cent the patient did not wish to communicate any evaluation concerning drugs or methods used. Obviously, because of the use of the amnesic agents, some parturients remembered nothing of labor or delivery. Such cases were coded excellent unless the parturient disclosed significant unpleasant symptoms resulting from the amnesia. When the patient remembered only single or occasional disjointed events of labor or delivery, the analgesia was coded as "good."

### Experimental Group

Since it was our object to evaluate the efficiency and safety of the various methods designated by the five groups in a controlled study, 1,489 parturients, or about 20 per cent of the total, were managed in the five groups by a chronological delineation from their hospital history numbers. These patients had their method of management chosen for them by the last two digits of their history numbers in the manner that all patients with numbers ending in 0 and 1 were managed by the Group I method; those with endings of 2 and 3 by Group II; those with endings 4 and 5 by Group III; those with endings 6 and 7 by Group IV; those with endings 8 and 9 by Group V. In this manner the human choice factor was eliminated. However, both the experimental group and the larger heterogeneous groups with complications or patients removed from the experimental group for any of the reasons listed in Table IV were analyzed in evaluating the various drugs and techniques. There was no significant difference in mothers' evaluations regardless of whether the physician or history number digits determined the method.

Therefore, the 1,489 patients without complications in either mother or baby group (which represented 20 per cent of the study, and which were managed by methods as determined by the terminal digits of their history numbers) are not studied in detail in this paper, but have been reported upon in the Dec. 1, 1953, Vol. 53, No. 53 issue of the *New York State Journal of Medicine*.

Instead, the entire group of 7,704 mothers who had single babies alive in utero before the onset of analgesia from both hospitals are herein reported upon.

### The Combined Total Group

The controlled obstetrical study at Hopkins covered deliveries during the period of November, 1948, through March, 1951. The Sinai study covered the period of October, 1949, through March, 1951.

Sixty-nine per cent of the infants at Sinai were born to private patients as against 26 per cent at Hopkins. There were five nonwhite infants delivered at Sinai as against 2,917 (51 per cent of total mothers) at Hopkins. By combining the total mothers in Tables II and III, we believe there is a more

representative sample of American obstetrics than would be the case in analyzing the cases of only one of the hospitals alone.

In Hopkins, 5,856 infants were delivered to 5,766 mothers; in Sinai, 3,616 infants were delivered to 3,581 mothers as recorded in Summary Table I.

The specific type of delivery was controlled on the basis of the last digit of the hospital history number among ward patients only unless one of the reasons presented in Tables IV and V required the withdrawing of the intended method and the substitution of an indicated method on the basis of either therapy, expediency, or complications inherent in the method.

The percentage of mothers retained in each of the three study groups at Sinai is higher than at Hopkins. This may be due to the large number of non-white mothers in the Hopkins' groups who frequently came to the hospital late in labor and more frequently in precipitate labor. In Table IV it can be seen that 1,287, or 30 per cent of the five groups combined, were precipitous labors, as against 207, or 18 per cent, at Sinai as recorded in Table V. Seventy-two per cent of the 1,287 were nonwhite mothers.

#### **Failure of Psychoanalgesia Among Ward Patients**

It is significant that in spite of the ideal labor-room environment already described 47 per cent of the ward patients designated by the history number digit method were failures in the psychoanalgesia method in which our staff attempted to conduct labor without analgesia or anesthesia with drugs. These patients became so miserable or uncontrollable with suggestion and attempted psychological lobotomy analgesia that it was necessary to substitute drug therapy for their own safety and the peace of the remainder of the hospital. This compared unfavorably with the 0.24 per cent failure rate in Group I; the 0.12 per cent failure rate in Group II; the 0.34 per cent failure rate in Group IV; and the 0.36 per cent failure rate in Group V. This fact is further accentuated by the psychological evaluations of the ward patients recorded in Table III which shows that only 69.5 per cent of 542 ward mothers remaining in the Group indicated 24 hours after delivery that they were satisfied with the management of their pain relief. When we combine the 165 dissatisfied ward mothers with the 388 ward mothers removed from the group as indicated in Table IV, a total of 558 of 820 mothers, or 67 per cent of the total, were failures or unsatisfactorily managed by this method. This compares unfavorably with better than 85 per cent success in spinal and caudal anesthesia.

This analysis explains somewhat the 93.2 and the 91.7 per cent satisfactory results from the patient standpoint described in the psychological evaluation of a small group of 101 mothers who elected with their obstetrician the psychoanalgesia technique as recorded in the private patient section of Table III. This table does not take into account the larger number of private patients who elected to "remain in this group method of management as long as possible" but who during the course of labor required and were given other forms of management using analgesic drugs and anesthetics.

Likewise, except among private patients, local anesthesia (pudendal block) succeeded in less than 70 per cent of 197 patients (Tables II and III).

TABLE IV. PERCENTAGE OF MOTHERS (WARD) WHO REMAINED IN OR WERE REMOVED FROM THE EXPERIMENTAL GROUPS AND THE REASON FOR REMOVAL (HOPKINS HOSPITAL)

REASON	PERCENTAGE					NUMBER*						
	TOTAL	GROUP I	GROUP II	GROUP III	GROUP IV	GROUP V	TOTAL	GROUP I	GROUP II	GROUP III	GROUP IV	GROUP V
Total ward patients	100	100	100	100	100	100	4,233	842	870	820	876	825
All substitutions	75.41	65.44	77.59	83.05	76.71	74.30	3,192	551	675	681	672	613
Precipitous labor	30.40	32.07	39.08	4.03	41.33	34.18	1,287	270	340	33	362	282
Fetal distress	.24	.12	.23	.49	.23	.12	10	1	2	4	2	1
Insufficient staff	.90	.95	.80	.12	1.14	1.46	38	8	7	1	10	12
Maternal complications	19.47	18.05	24.48	18.90	17.70	18.06	824	152	213	155	155	149
Inertia, intrinsic	1.30	1.19	1.26	.61	1.83	1.58	55	10	11	5	16	13
Inertia, extrinsic	.14	—	.23	.12	.11	.24	6	—	2	1	1	2
Prematurity	4.91	6.29	5.17	5.00	4.79	3.27	208	53	45	41	42	27
Research	1.37	1.54	1.38	1.95	1.03	.97	58	13	12	16	9	8
Teaching	.92	1.07	.92	1.34	1.14	.12	39	9	8	11	10	1
Error	1.65	2.02	1.95	.98	2.17	1.09	70	17	17	8	19	9
Failed insertion	2.06	—	.35	—	2.74	7.27	87	—	3	—	24	60
Drug failure	.17	—	.12	—	.11	.61	7	—	1	—	1	5
Vomited	.05	.12	.12	—	—	—	2	1	1	—	—	—
Analgesia indicated	1.04	.12	.12	1.46	.23	3.40	44	1	1	12	2	28
Failure, method	9.38	.24	.12	47.32	.34	.36	397	2	1	388	3	3
Patient refused method	.87	.83	.57	.49	1.14	1.33	37	7	5	4	10	11
Unknown reason†	.54	.83	.69	.24	.68	.24	23	7	6	2	6	2
Experimental group	24.59	34.56	22.41	16.95	23.29	25.70	1,041	291	195	139	204	212

Group:

- I—Sedation-inhalation,
- II—Sedation-intravenous,
- III—Psychoanalgesia,
- IV—Sedation-terminal block,
- V—Continuous conduction.

\*Excludes second twins (81).

†Includes 6 infants who died before labor and analgesia but no substitution reason was given.

TABLE V. PERCENTAGE OF MOTHERS (WARD) WHO REMAINED IN OR WERE REMOVED FROM THE EXPERIMENTAL GROUPS AND THE REASONS FOR REMOVAL (SINAI HOSPITAL)

REASON	PERCENTAGE				NUMBER*			
	TOTAL	GROUP A	GROUP B	GROUP C	TOTAL	GROUP A	GROUP B	GROUP C
Total ward patients	100	100	100	100	1,121	451	337	333
All substitutions	60.04	48.12	69.73	66.37	673	217	235	221
Precipitous labor	18.47	19.73	23.14	12.01	207	89	78	40
Fetal distress	.18	—	—	.60	2	—	—	2
Insufficient staff	10.08	.45	12.46	20.72	113	2	42	69
Maternal complications	12.22	9.54	14.54	13.52	137	43	49	45
Inertia, intrinsic	.45	—	.89	.60	5	—	3	2
Inertia, extrinsic	.27	—	.59	.30	3	—	2	1
Prematurity	6.96	8.87	2.67	8.71	78	40	9	29
Research	.53	.45	.30	.90	6	2	1	3
Teaching	4.55	5.54	2.08	5.71	51	25	7	19
Error	1.34	.67	2.08	1.50	15	3	7	5
Failed insertion	2.14	1.33	5.34	—	24	6	18	—
Drug failure	.89	.44	2.08	.30	10	2	7	1
Vomited	—	—	—	—	—	—	—	—
Analgesia indicated	.62	.44	1.18	.30	7	2	4	1
Failure	—	—	—	—	—	—	—	—
Patient refused method	1.07	.44	2.08	.90	12	2	7	3
Unknown reason†	.27	.22	.30	.30	3	1	1	1
Experimental group	39.96	51.88	30.27	33.63	448	234	102	112

Group:

A—Sedation—terminal block,

B—Continuous conduction,

C—Sedation—inhalation or intravenous.

\*Excludes second twins (12).

†Includes 2 infants who died before labor but no substitution reason was given.

**Substantiation of Necessity of Pain Relief in Childbirth from Britain**

This analysis is entirely in line with the evaluation given by 196 British women doctor-mothers. The British Council of the Medical Women's Federation asked 300 doctor-mothers: Is relief of pain in childbirth necessary? The overwhelming response, reported by the *British Medical Journal*: Yes. Of 196 who replied, 184 were in favor of drugs in the delivery room; only 8 were definitely against. The women who answered have a combined experience of 425 confinements. Of these 66 per cent were in hospitals or nursing homes, where it is easier to relieve pain; only 28 per cent were at home. But 21 to 36 per cent wanted more than they got.

There was no doubt in the mind of the author of the report, Dr. Kitty Kate Conrad, 39, mother of two. Said she: "Even when one has seen 300 or more confinements, as I have, the severity of labor pains comes as an intense surprise. They are more exereuciating than anything you can possibly imagine. I am certainly in favor of spreading the use of pain-relieving drugs in childbirth as widely as possible." Some of our patients in their recorded comments were in complete agreement with Dr. Conrad. Some of them even agreed with the red-haired Labor Parliament member of Britain, Mrs. Leah Manning: "If some doctors had a labor ward of men to look after, I think it highly probable that for the defense of their sanity they would give their patients something more than a towel and tell them to pull on it."



However, in defense of the no anesthesia or analgesia method we found enthusiastic supporters among the 101 of 3,497 private patients and among some of the 114 of the 820 ward patients. The small minorities in both extremes of the question for and against pain relief in obstetrics with analgesic and anesthetic drugs demonstrated a proficiency in verbalization. In between the extremes were the masses of women with a decided, though moderate, leaning toward the use of analgesics and anesthetics in childbirth.

### Significance of the Subject in the United States

The mere mention of the approximately 4,000,000 births per year in the United States, with use of some form of pain-relieving drugs in more than 75 per cent of them, indicates the importance of the subject. With an average \$15.00 consideration to hospital or physician for each obstetrical anesthetic there is a total investment made by three million women of approximately \$45,000,000 in America for this service. It is interesting to reflect on the fact that this represents 24,000,000 women hours in labor if the conservative figure of six hours of labor per average case is standard. By way of comparison, the 535 members of both Houses of Congress spend approximately 200 eight-hour days in each session for a total of 800,000 Congressman hours or approximately 3 per cent of the time deliberating the Nation's present as the maternal population spends in actual labor producing the population foundation of the Nation's future.

TABLE VI. LABOR. PERCENTAGE OF SPECIFIED DRUG GIVEN IN LABOR OR DELIVERY THAT IS EVALUATED UNSATISFACTORY BY MOTHERS\* (HOPKINS AND SINAI)

NAME OF DRUG ALONE OR AUGMENTED	PERCENTAGE			NUMBER†		
	BOTH HOSPITALS	HOPKINS	SINAI	BOTH HOSPITALS	HOPKINS	SINAI
Demerol	13.67	18.81	11.21	3,050	989	2,061
Metycaine	13.71	15.93	12.00	3,166	1,375	1,791
Seconal	13.97	18.43	10.38	2,734	1,221	1,513
Scopolamine	14.18	17.59	11.73	3,943	1,649	2,294
Nupercaine	16.06	21.25	13.57	741	240	501
Nembutal	17.54	19.82	14.77	2,012	1,105	907
Xylocaine	19.48	18.53	22.22	349	259	90
Pentothal sodium	19.58	20.33	12.50	669	605	64
Pontocaine	19.78	22.66	17.46	455	203	252
Nitrous oxide, ether	21.06	24.46	12.59	1,439	1,026	413
Nitrous oxide (no ether)	27.44	30.53	14.90	1,290	1,035	255

\*Excludes mothers of twins.

†Excludes mothers with unknown or no evaluation.

### Evaluation of the Efficiency of Drugs and Anesthetics

All of the presently used analgesic and anesthetic drugs were used in this study including methadone, Nisentil, heroin, paraldehyde, cyclopropane, Surital, chloroform, and Cyclaine in addition to those listed in Tables VI and VII. However, when an agent was used less than 50 times, it was not included in this study. It should be pointed out that cyclopropane, administered 20 times during delivery in our hospitals, was definitely a superior agent, but, because of the lack of adequate explosion-proof environment, it was not used as a

major agent. Trichlorethylene was administered 45 times with 6 mothers, or 15.4 per cent, reporting unsatisfactory results.

TABLE VII. DELIVERY. PERCENTAGE OF MOTHERS BY PSYCHOLOGICAL EVALUATION WHEN ONLY ONE SPECIFIED DRUG WAS ADMINISTERED DURING DELIVERY (HOPKINS AND SINAI)

DRUGS DURING DELIVERY	PERCENTAGE		NUMBER		
	SATIS-FACTORY	UNSATIS-FACTORY	MOTHERS' KNOWN REPORT*	SATIS-FACTORY	UNSATIS-FACTORY
<i>Inhalation.</i> —					
Nitrous oxide, oxygen	73.97	26.03	803	594	209
Nitrous oxide, ether, oxygen	79.27	20.73	1,283	1,017	266
Trichlorethylene	84.60	15.40	45	39	6
<i>Intravenous.</i> —					
Pentothal sodium	81.60	18.40	413	337	76
<i>Continuous Conduction (Caudal or Peridural).</i> —					
Metycaine	88.50	11.50	1,148	1,016	132
Pontocaine	83.06	16.94	124	103	21
Xylocaine	84.26	15.74	108	91	17
<i>Terminal Block (Saddle Block or Spinal).</i> —					
Procaine	88.71	11.29	62	55	7
Metycaine	88.82	11.18	1,368	1,215	153
Pontocaine	85.21	14.79	169	144	25
Nupercaine	85.11	14.89	658	560	98
Xylocaine	91.43	8.57	35	32	3

\*Cesarean sections, twins, and infants who died before labor are excluded.

Fig. 2 presents the graphic incidence of unsatisfactory evaluation by the mothers of the eleven major agents used in this study. In this study it is evident that nitrous oxide alone during anesthesia whether or not superimposed upon preliminary sedation in labor gave the highest incidence of unsatisfactory reports from the mothers. It should be emphasized here that the techniques used here always maintained the oxygen at 20 per cent or above. These techniques were used in complete accord with the pioneer studies of Eastman which first showed that "if the concentration of oxygen is less than 15 to 20 per cent, anoxemia of the fetus results. Furthermore, prolonged use of this gas in higher concentrations may result in fatal maternal accidents as shown by Courville, Lowenberg and others." The use of nitrous oxide:oxygen in a 90:10 mixture for five minutes reduces the oxygen saturation of the arterial blood of the fetus from 40 to 20 per cent and the oxygenation of the venous blood from 8 to approximately 2 per cent. Clinically, we became aware of the fact that the robust mother with normal hemoglobin in intense pain in the second stage of labor was frequently unsubdued to an adequate plane of anesthesia for delivery with mixtures of 80:20 nitrous oxide-oxygen even after 15 minute inductions. The patients themselves listed "oppressive dizziness," "frightful dreams," and "pain in subconsciousness" as major disadvantages of this agent.

The addition of ether analgesia or the substitution of ether anesthesia or the addition of Trilene analgesia to the mixture considerably improves the efficiency of nitrous oxide in patient acceptance in providing relaxation for

difficult operative delivery. Yet the reactions of these mothers who reported 27 per cent unsatisfactory results with this agent should not be taken lightly even though the procedure was safe. The words of Munroe Kerr and Chassar Moir should be re-emphasized: "Of this it may be said that it is no triumph of obstetric art to deliver a woman safely but to leave her mind so full of vivid and unhappy memories that she refuses to face childbirth again."

### Evaluation of Analgesic Drugs for Delivery

Scopolamine to produce amnesia was used widely in this study in average total doses of 1.5 mg. of scopolamine for each labor. Fig. 3 and Table VIII present the efficiency of the various agents combined with scopolamine.

With Seconal alone there was a very high incidence, 26 per cent of those who became agitated with complete loss of frontal-lobe control. This lack of good analgesia was reduced significantly by the substitution of Demerol or Nembutal, and reduced still further by the use of balanced analgesia with

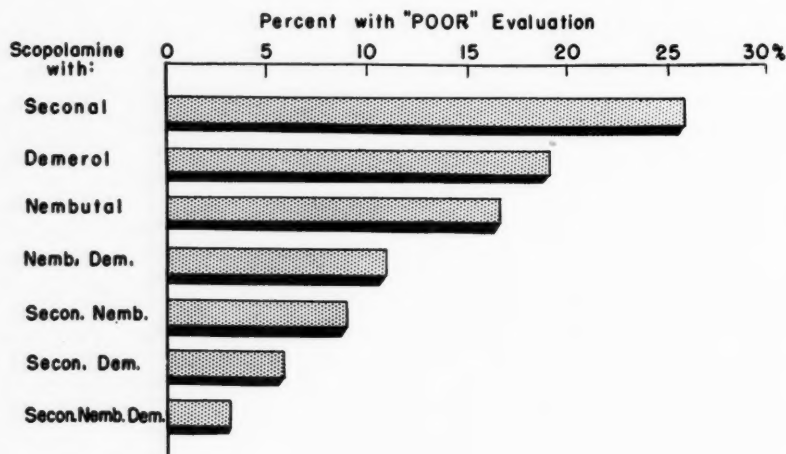


Fig. 3.

TABLE VIII. PERCENTAGE OF SPECIFIED DRUG GIVEN IN LABOR OR DELIVERY THAT IS EVALUATED UNSATISFACTORY BY MOTHERS\* (HOPKINS AND SINAI)

NAME OF DRUG ALONE OR AUGMENTED	PERCENTAGE			NUMBER†		
	BOTH HOSPITALS	HOPKINS	SINAI	BOTH HOSPITALS	HOPKINS	SINAI
Demerol	13.67	18.81	11.21	3,050	989	2,061
Metycaine	13.71	15.93	12.00	3,166	1,375	1,791
Seconal	13.97	18.43	10.38	2,734	1,221	1,513
Scopolamine	14.18	17.59	11.73	3,943	1,649	2,294
Nupercaine	16.06	21.25	13.57	741	240	501
Nembutal	17.54	19.82	14.77	2,012	1,105	907
Xylocaine	19.48	18.53	22.22	349	259	90
Pentothal sodium	19.58	20.33	12.50	669	605	64
Pontocaine	19.78	22.66	17.46	455	203	252
Nitrous oxide, ether	21.06	24.46	12.59	1,439	1,026	413
Nitrous oxide (no ether)	27.44	30.53	14.90	1,290	1,035	255

\*Excludes mothers of twins.

†Excludes mothers with unknown or no evaluation.

scopolamine for amnesia, Seconal or Nembutal for soporific effect, and Demerol for analgesia. The highest incidence of success was obtained with 100 mg. of Nembutal intravenously at the onset of active labor, 100 mg. of Seconal by mouth; 100 mg. of Demerol intramuscularly, and 0.6 mg. of scopolamine intramuscularly with a repetition of 0.2 mg. of scopolamine each 2 hours. In this latter series the number with poor evaluation fell to 3 per cent. Of course, as the amount of analgesia and systemic narcosis increased, the more delayed became the breathing and crying time of the infants, as has been reported in other parts of this study.

TABLE IX. METHOD OF DELIVERY FOR MOTHERS BY PRIVATE PHYSICIAN  
(JOHNS HOPKINS)

PHYSICIAN BY CODE NUMBER	TOTAL* MOTHERS	METHOD OF DELIVERY						
		NO DRUG	INHALA- TION	INTRA- VENOUS	LOCAL	CAUDAL	SPINAL	PERI- DURAL
<i>Percentage.—</i>								
Total	100	3.3	38.7	12.2	2.2	30.0	13.4	0.2
1	100	4.2	27.3	13.2	6.2	38.4	10.4	0.3
2	100	4.2	45.8	3.4	0.8	31.7	13.3	0.8
3	100	2.1	8.5	28.7	—	25.6	34.6	0.5
4	100	7.9	34.5	12.2	1.3	38.4	5.7	—
5	100	0.4	39.1	13.0	0.9	35.7	10.9	—
6	†							
7	†							
8	100	—	76.5	—	—	5.9	17.6	—
9	100	1.2	77.1	2.5	0.4	8.2	10.6	—
<i>Number.—</i>								
Total	1,418	47	549	173	31	425	190	3
1	385	16	105	51	24	148	40	1
2	120	5	55	4	1	38	16	1
3	188	4	16	54	—	48	65†	1
4	229	18	79	28	3	88	13	—
5	230	1	90	30	2	82	25	—
6	1	—	1	—	—	—	—	—
7	3	—	1	—	—	—	2	—
8	17	—	13	—	—	1	3	—
9	245	3	189	6	1	20	26	—

\*Excludes all cesarean sections.

†Less than 10 deliveries.

‡One maternal death, thrombus and/or embolus.

### The Parturient's Evaluation of Each Physician by Method of Pain Relief

As drugs and anesthetics vary in action in different patients, so do physicians in their personalities, patient acceptability, and efficiency in the use of the various methods. Carl Gauss who developed *dämmerschlaß* said in 1913: "Show me the average woman, and I will show you the average dose, but since there is no average woman, there is no average dose." From the standpoint of safety and efficiency, we are convinced that the various drugs and methods are no more safe and efficient than the men who use them. There were nine obstetricians on the private service in the Johns Hopkins Hospital. Each one of them was assigned a blind number on the IBM card so that the psychologist could interview and record the data from each private patient without know-



ing the name of the obstetrician. In this manner, another personal factor was eliminated. As can be seen by Table IX, there was wide variation in the individual physician's choice of agents and techniques for his patients. One physician used inhalation agents in 77 per cent and intravenous agents in 2.5 per cent, while another physician used inhalation agents in 8.5 per cent and intravenous agents in 28.7 per cent, and caudal in 25.6 per cent. The highest use of no drug during labor or delivery among all of the obstetricians was 7.9 per cent, while all of them were encouraged to try the method occasionally.

TABLE X. PSYCHOLOGICAL EVALUATION FOR EACH PHYSICIAN BY METHOD OF DELIVERY  
(JOHNS HOPKINS)

METHOD OF DELIVERY	PERCENTAGE		NUMBER		
	SATISFACTORY	UNSATISFACTORY	TOTAL* MOTHERS	SATISFACTORY	UNSATISFACTORY
<i>Physician No. 1.—</i>					
Total	85.6	14.4	360	308	52
No drugs	85.7	14.3	14	12	2
Inhalation	79.8	20.2	99	79	20
Intravenous	93.5	6.5	46	43	3
Local	95.0	5.0	20	19	1
Caudal	88.7	11.3	141	125	16
Spinal	76.9	23.1	39	30	9
Peridural	—	†	1	—	1
<i>Physician No. 2.—</i>					
Total	94.7	5.3	113	107	6
No drugs	†	—	5	5	—
Inhalation	94.3	5.7	53	50	3
Intravenous	†	†	4	3	1
Local	†	—	1	1	—
Caudal	94.3	5.7	35	33	2
Spinal	100.0	—	14	14	—
Peridural	†	—	1	1	—
<i>Physician No. 3.—</i>					
Total	91.1	8.9	168	153	15
No drugs	†	—	4	4	—
Inhalation	87.5	12.5	16	14	2
Intravenous	85.7	14.3	42	36	6
Local	95.7	4.3	46	44	2
Caudal	—	—	—	—	—
Spinal	93.2	6.8	59	55	4
Peridural	—	†	1	—	1

\*Excludes 28 cesarean sections for No. 1; 8 cesarean sections for No. 2; 20 cesarean sections for No. 3.

†Less than 10 deliveries.

Tables X, XI, and XII present the parturients' psychological grading of the methods of pain relief of each physician. The high rating of satisfactory results of better than 85 per cent in the averages of all physicians, regardless of method used, points out the merit of the high type of competence in private practice in this hospital. Two physicians achieved the near perfect score of better than 96 per cent satisfied patients in regard to their methods of pain relief. The lowest score of 75 per cent for a single technique was given the physician by 24 patients delivered by him under intravenous anesthesia. This

TABLE XI. PSYCHOLOGICAL EVALUATION FOR EACH PHYSICIAN BY METHOD OF DELIVERY  
(JOHNS HOPKINS)

METHOD OF DELIVERY	PERCENTAGE		NUMBER		
	SATISFACTORY	UNSATIS- FACTORY	TOTAL* MOTHERS	SATISFACTORY	UNSATIS- FACTORY
<i>Physician No. 4.—</i>					
Total	85.6	14.4	216	185	31
No drugs	94.1	5.9	17	16	1
Inhalation	82.4	17.6	74	61	13
Intravenous	75.0	25.0	24	18	6
Local	†	†	3	1	2
Caudal	90.8	9.2	87	79	8
Spinal	90.9	9.1	11	10	1
Peridural			—		
<i>Physician No. 5.—</i>					
Total	88.1	11.9	210	185	25
No drugs	†	—	1	1	—
Inhalation	82.7	17.3	81	67	14
Intravenous	88.5	11.5	26	23	3
Local	†	—	2	2	—
Caudal	93.8	6.2	80	75	5
Spinal	85.0	15.0	20	17	3
Peridural			—		
<i>Physician No. 6.—</i>					
Total	†	—	1	1	—
Inhalation	†	—	1	1	—
<i>Physician No. 7.—</i>					
Total	†	—	3	3	—
Inhalation	†	—	1	1	—
Spinal	†	—	2	2	—

\*Excludes 11 cesarean sections for No. 4; 17 cesarean sections for No. 5.

†Less than 10 deliveries.

TABLE XII. PSYCHOLOGICAL EVALUATION FOR EACH PHYSICIAN BY METHOD OF DELIVERY  
(JOHNS HOPKINS)

METHOD OF DELIVERY	PERCENTAGE		NUMBER		
	SATISFACTORY	UNSATIS- FACTORY	TOTAL* MOTHERS	SATISFACTORY	UNSATIS- FACTORY
<i>Physician No. 8.—</i>					
Total	87.5	12.5	16	14	2
Inhalation	91.7	8.3	12	11	1
Caudal	—	†	1	—	1
Spinal	†	—	3	3	—
<i>Physician No. 9.—</i>					
Total	96.3	3.7	218	210	8
No drugs	†	—	2	2	—
Inhalation	95.9	4.1	169	162	7
Intravenous	†	—	6	6	—
Local	†	—	1	1	—
Caudal	94.4	5.6	18	17	1
Spinal	100.0	—	22	22	—
Peridural			—		

\*Excludes 14 cesarean sections for No. 9.

†Less than 10 deliveries.

same physician attained the highest rating with his 17 patients who used not a single milligram of narcotic or anesthetic drug during labor or delivery and whose method was recorded as satisfactory in 16 instances. More than 90 per cent of his patients delivered by caudal and spinal anesthesia were satisfied. This physician represents the type of personality who is at his best when his patients are awake and are a part of the thrilling events surrounding the delivery of the baby.

### Summary and Conclusions

1. The parturients themselves who experience labor and delivery should be given more opportunity to evaluate the efficiency of methods of analgesia.

2. The majority of women in America, regardless of propaganda to the contrary, desire and require and deserve analgesia and anesthesia during labor and delivery. Certainly it is just as safe in most cases and safer in many to mother and baby to have the advantages of pain relief in childbirth in modern obstetrics.

3. Cognizant of the wishes of women who neither request nor require pharmacological anesthesia or analgesia, the obstetricians and anesthesiologists must understand psychoanalgesia also and carry it as far as is expedient without prejudice, yet always have close at hand the anesthesia so often required unexpectedly in obstetrics.

4. There is a hard core of parturients at present of 4 to 12 per cent in private practice and 12 to 25 per cent in ward practice as yet unsatisfactorily relieved or managed, from their standpoint, during labor and delivery. As new equipment and skills and techniques are developed, this is the group requiring renewed efforts compatible with safety to make them comfortable.

5. It is evident from the reactions of the patients that more comfortable and pleasant environment embodying air-conditioning in extremely hot weather, interior decorating, lighting, and therapeutic music is sometimes as important as doses of the narcotic.

6. The physician who administers the drugs and anesthetics and manages parturition is just as important as the ratio of the recipe in the mind of the parturient.

## TWO THOUSAND DELIVERIES UNDER A TRAINING FOR CHILDBIRTH PROGRAM

### A Statistical Survey and Commentary

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**D**R. KOSMAK'S interest in the subject upon which we write is seen in his comment concerning programs designed to prepare women for childbirth, psychologically and physically. He has said, "There has come about a gradual awakening in recent years and it is to be hoped that a new era is being born in which patients as well as doctors may realize that the less artificiality enters the process of childbearing the better the final result. This will be a gradual process. It will require time and the exercise of much patience and in, say, another decade we may survey the results on a basis of further factual information. . . ." The subject is an important one for it has wide implications. It involves not only the safety and well-being of mother and child, but the establishment of family life.

In 1951 this Clinic reported observations on "One Thousand Consecutive Deliveries Under a Training for Childbirth Program."<sup>2</sup> These were of women delivered between Jan. 1, 1949, and March 31, 1950, on the University Service of the Grace-New Haven Community Hospital, and represented consecutive deliveries of all patients who had infants weighing 1,500 grams or over. All women were cared for under a regime in which we emphasize educational preparation for childbirth and increased personal attention during labor, which seeks to encourage and assist the parturient woman to use to her advantage the natural forces of labor. To quote from the previous communication, "To carry out these aims we attempt to prepare women for childbirth psychologically and physically by means of a training program in which they are taught the fundamentals of reproductive anatomy and physiology and, also, are trained in relaxation techniques and muscle control to aid the natural forces of labor. In labor they are encouraged to use this knowledge and training by those who are in attendance. The conduct of labor and delivery without analgesia or anesthesia is definitely not our primary aim. Our interest is rather directed toward assuring each woman a psychologically and emotionally satisfying labor experience, and one which is at the same time physically safe for both mother and child. We believe that a conscious delivery can be the source of a great sense of achievement for most women—and that in a normal labor, properly conducted, in a woman who has been prepared for the experience, much of the unnecessary pain,



which is usually experienced, can be prevented. As the result, small amounts of medication suffice. We do not contend that relaxation alone will prevent all pain—even in most women—nor that pain is in any sense a desirable or beneficial part of the childbearing experience. For episiotomy and perineal repair we routinely use 2 per cent Novocaine infiltration, seldom finding it necessary to do pudendal block. Our indications for forceps are those generally accepted and we prefer low spinal anesthesia for most instances of such procedure.”

The program is a joint enterprise shared with the Pediatric Department of the Hospital. To Dr. Milton J. E. Senn, Dr. Edith B. Jackson, and their associates, full credit must be given. From the beginning the experience has been a happy coalescence of mutual interests.

The results in these first 1,000 deliveries are recapitulated.

1,000 CONSECUTIVE DELIVERIES, JAN. 1, 1949, TO MARCH 31, 1950  
1,014 infants (1,500 grams or over)

CLINIC STATUS			
Ward		779	women
Semi-private and private		221	women
PARITY			
Primiparas		375	
Multiparas		625	
TYPES OF DELIVERY			
	PRIMIPARAS	MULTIPARAS	
Spontaneous 881 (88.1 per cent)	292	589	
Operative total 119 (11.9 per cent)	83	36	
Vaginal operative 78 (7.8 per cent)		60	18
Cesarean section 41 (4.1 per cent)		23	18
LENGTH OF LABOR			
Primiparas—total length of labor, mean (average)	14.3	hours—median	11 hours.
Multiparas—total length of labor, mean (average)	8.0	hours—median	6.9 hours.
Average length of total labor, both groups,	10.3	hours.	
INFANT DEATHS			
Antepartal—4 (delivered spontaneously)			
Intrapartal—4 (spontaneous 1, operative 3)			
Neonatal—4 (spontaneous 3, operative 1)			

The foregoing results supplement the present report of another series of 1,000 women delivered on the University Service between Oct. 1, 1950, and March 30, 1952. These deliveries also represent a series essentially consecutive. A few records in sequence were not available. Some unselected case reports were therefore added.

Although classes are available for all registered women, not all have participated. Some have attended a portion of the course, others not at all. In the series there were 40 women (4 per cent) who were unregistered and seen for the first time in labor. In all deliveries, however, we endeavor to give the attention and support which we have referred to.

CLINIC STATUS OF 1,000 WOMEN (SECOND SERIES)

Ward	667
Private and semiprivate	333

PARITY

Primiparas	328
Multiparas	672

TYPE OF DELIVERY

	PRIMIPARAS	MULTIPARAS
Spontaneous 880 (88.0 per cent)	258 (78.0 per cent)	622 (92.5 per cent)
Operative (total) 120 (12.0 per cent)	70	50
Vaginal operative 88 (8.8 per cent)	62	26
Cesarean section 32 (3.2 per cent)	8	24

ANALGESIA AND ANESTHESIA

*Analgesia.*—

In 968 vaginal deliveries 302, or 31 per cent, did not require an analgesic during labor. In 451, or 46 per cent, a single dose was given of Demerol or Seconal (not more than 100 mg.). In 215, or 22 per cent, a combination of two drugs or more than one dose of the same agent was given.

*Anesthesia.*—

179 women had no second-stage anesthesia.

789 women had intermittent Trilene or nitrous oxide inhalations.

296 women had local or pudendal block.

59 women had a major type of anesthesia, either general or spinal. These include those women delivered by cesarean section.

In the whole group only 47 women (2 primiparas, 45 multiparas) went through labor and delivery without analgesia and anesthesia.

DURATION OF LABOR

*First Stage.*—

*Primiparas:* In one instance of the 258 primiparas, length of labor was not recorded. In 34 per cent of 257 the first stage was 6 hours or less. In 63 per cent it was 10 hours or less. Eleven primiparas delivered spontaneously after a first stage exceeding 24 hours. In 50 per cent of the primiparas delivered by operation the first stage was complete in 10 hours or less. Four women in the operative group had a first stage of 24 hours or over.

*Multiparas:* In 6 of the 622 multiparas the duration of the first stage was not recorded. In 40 per cent of 616 the first stage was under 4 hours. In 60 per cent it was less than 6 hours. Only 8 women had a first stage lasting over 24 hours. Of the 26 multiparas who had operative vaginal deliveries only 3 had a first stage over 9 hours.

*Second Stage.*—

*Primiparas:* Fifty-seven and five-tenths per cent of the primiparas who delivered spontaneously had a second stage of 40 minutes or less. Fifteen and one-tenth per cent had a second stage of over 1 hour.

*Multiparas:* Of 622 multiparas, in 27 instances no record of the second stage is available. In 595 women, 54 per cent had a second stage of less than 15 minutes. Twelve women had one of more than 1 hour but less than 2. In multiparas (18) delivered by vaginal operation, in 6 the second stage was longer than 1 hour. In none was it more than 2 hours.

*Third Stage.*—

*Primiparas:* In 68.1 per cent of primiparas delivered spontaneously the third stage was less than 8 minutes. In 7.3 per cent the third stage was over 20 minutes. In primiparas delivered by vaginal operation 64.5 per cent had a third stage less than 8 minutes and in 6.0 per cent this time was over 20 minutes.

*Multiparas:* In 62.0 per cent the third stage was less than 5 minutes and in 14.0 per cent it was longer than 20 minutes.

*Total Length of Labor.—**Primiparas:*

258 women delivered spontaneously.

49.0 per cent in less than 10 hours

78.0 per cent in less than 15 hours

4.2 per cent in over 24 hours

15 women delivered "precipitately."

62 women delivered by vaginal operation. In 82 per cent the total labor was less than 17 hours.

*Multiparas:* There were 622 spontaneous deliveries. In 68.0 per cent, the total labor was less than 7 hours. In 17.7 per cent of the cases of precipitate or short labor no record was made. In 0.9 per cent the labor lasted over 24 hours.

In 26 vaginal operative deliveries all but 1 patient delivered within 13 hours.

*Summary of Length of Labor.—*

In 968 women delivered vaginally, 12.9 per cent had very short or precipitate labors. Only 2.3 per cent had labors longer than 24 hours, 52.7 per cent of the entire group delivered within 6 hours.

## RESULTS FOR THE INFANT

To 1,000 mothers 1,010 infants (over 1,500 grams) were born. There were 10 twin pregnancies. Of the 1,010 infants 78 weighed less than 2,500 grams at birth.

In this second series there were 18 fetal deaths. Ten were recorded as antenatal, 5 as intrapartum, and 3 as neonatal.

*Antenatal Deaths, 10.—*

The 10 chief contributing factors were listed as: (1) prematurity, (2) prematurity, (3) macerated twin, (4) prematurity, (5) erythroblastosis fetalis, (6) erythroblastosis fetalis, (7) hydrops fetalis, (8) unknown, (9) prematurity, (10) unknown.

*Intrapartum Deaths, 5.—*

The 5 chief contributing factors were listed as: (1) prematurity, (2) prematurity, (3) version and extraction for right mentum anterior, (4) hydrocephalus (destructive operation), (5) hydrocephalus (destructive operation).

*Neonatal Deaths, 3.—*

The 3 chief contributing factors were listed as: (1) prematurity, (2) prematurity, (3) congenital anomalies.

Thus in 8 infants prematurity was considered the direct or contributing cause of death. Rh incompatibility was present in the mothers of 4 infants, 3 of whom showed severe erythroblastosis fetalis. In 4 infants congenital anomalies were present which were incompatible with life.

The chief concern from the standpoint of fetal salvage is obviously prematurity. The findings show that of the 78 mothers who had infants weighing less than 2,500 grams at birth, 15 showed some grade of anemia, 14 had toxemia, 13 had previously had abortions, 2 had nephritis, 1 had active tuberculosis, 2 had inactive rheumatic heart disease, 1 had a positive serologic test for syphilis.

## BLOOD LOSS

It is our confirmed opinion that blood loss following delivery has been less since the inauguration of the program. We attribute this in great part to the relatively shorter labors and the lessened use of analgesic and anesthetic agents.

In surveying our results in this second 1,000 deliveries we should state that blood loss on our service is estimated and not measured. Whenever blood loss is estimated at 300 c.c. or over, we consider it as abnormal. In 112 instances the blood loss was estimated from 300 to 499 c.c. (35 primiparas or 10.6 per cent, 77 multiparas or 11.3 per cent). In 32 instances, or 3.2 per cent of the entire group, the blood loss was estimated at over 500 c.c.

# CESAREAN SECTION

There were 8 cesarean sections in primiparas and 24 in multiparas. In this latter group 14 were repeat sections. The incidence of primary section for the 1,000 deliveries was 18 or 1.8 per cent.

## COMBINED RESULTS IN THE TWO SERIES (2,000 DELIVERIES)

2,000 women delivered  
2,024 infants (birth weight 1,500 grams or over)  
164 infants weighed less than 2,500 grams at birth  
22 instances of twin birth  
1 instance of triplet birth

## CLINIC STATUS OF WOMEN

Ward	1,446
Private and semiprivate	554

## PARITY

Primiparas	702
Multiparas	1,297

## TYPE OF DELIVERY

	PRIMIPARAS	MULTIPARAS
Spontaneous 1,761 (88.1 per cent)	550	1,211
Operative (total) 239 (11.9 per cent)	153	86
Vaginal operative 166 (8.3 per cent)	122	44
Cesarean section 73 (3.6 per cent)	31	42

## ANALGESIA AND ANESTHESIA—1,927 VAGINAL DELIVERIES

### *Analgesia.*—

No analgesic was given in 660 deliveries, or 34.2 per cent. A single dose of Demerol or Seconal (not more than 125 mg.) was given in 1,195 instances or 62.0 per cent.

### *Anesthesia.*—

In 562 women (29.1 per cent) no second-stage anesthetic was given.

In 1,275 women (66.1 per cent) second-stage anesthesia was limited to intermittent Trilene or nitrous oxide inhalations.

In 123 women a major type of anesthesia, either general or spinal, was administered. These include those delivered by cesarean section.

## RESULTS FOR THE INFANT

### *2,024 Infants Delivered (1,500 Grams or Over).*—

Antenatal infant deaths	18
Intranatal infant deaths	8
Neonatal infant deaths	4

This is a total of 30 infant deaths, or 1.43 per cent (uncorrected) in the 2,000 deliveries.

In presenting this report we have limited it to that material which we believe has a relationship to the training program. It is our hope that it will have value for comparison with results elsewhere where no similar program is being carried out. Our own experience has convinced us that under our present regime we have a greatly lessened number of depressed infants at birth, a decrease in length of labors, fewer operative deliveries, less blood loss, smoother convalescence, and, finally, happier mothers.



With regard to the latter, we recognize values gained which are not subject to the ordinary methods of statistical appraisal. The enthusiasm of wives and husbands for this type of care, which includes rooming-in if desired, has been part of a rewarding experience to all who have participated in its administration. The result has been the development of a greater combined effort on the Obstetric and Pediatric Services in teamwork which begins to function for each patient from the time of her first prenatal visit.

We are well aware of criticisms of our program. Many of these are not valid because of a misunderstanding of our aims and practices. A criticism which we do recognize as having validity relates to economics. To function well, such a program involving classes, exercise groups, increased personal attention during labor and in rooming-in procedures, does require more time on the part of doctors and nurses. It does involve some increase in nursing personnel. The cost of this is made up to a considerable degree by fees for classes, which all patients above the ward group seem glad to pay. Considering the results we are convinced that the added effort and expense are warranted. The doctors and nurses who have participated have found greater satisfaction in working under such a regime. Patients, particularly multiparas who have had a different experience previously, have expressed appreciation of efforts to give them more personal professional care during the intranatal and postnatal periods. We believe that the chief reason for these satisfactions is to be found in a better and more comprehensive viewpoint of what good obstetric and pediatric care really involves. Certain it is that there is an ever-widening interest on the part of our society in child-bearing and child rearing. The roles of the obstetrician and the pediatrician as guiding influences in future developments are of highest importance.

We gratefully acknowledge the assistance of Dr. Edward H. G. Hon in the preparation of material for this paper.

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## CONGENITAL UTERINE ANOMALIES AND ASSOCIATED COMPLICATIONS OF PREGNANCY

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**A**NOMALIES of the genital tract have been considered as anatomical curiosities chiefly because of their rare occurrence. In recent years, several clinical investigators have focused attention upon these abnormalities. Consequently they are now viewed as warranting serious consideration.

Abnormalities of the urinary and reproductive systems are intimately associated and they may give rise to various clinical conditions. In addition, when these congenital irregularities occur in association with pregnancy, they have been found to have considerable bearing upon the problems of abortion, premature labor, abnormalities of fetal presentation, and complications of the immediate postpartum period.

### Embryology

It is not our intention to deviate from a clinical study. However, there are certain basic facts which should be emphasized. Since the abnormalities of the reproductive and urinary systems are intimately associated in their development, it is advisable to consider the embryology of these two systems together. Both arise from the mesoderm of the intermediate cell mass. This unites the primitive segments with the lateral layers of the somatic and splanchnic mesoderm. In vertebrates, three distinct types of excretory organs develop in succession, each caudad to the other. The pronephros is evident at the fourth week of embryonic life and this is superseded by the mesonephros, or Wolffian body; this develops as the pronephros regresses.

The developing mesonephric tubules begin to differentiate, expand, and bulge ventrally in the celom, thus producing on each side of the dorsal mesentery of the mesonephros the urogenital fold. This extends from the fourth cervical to the third lumbar segments. This ridge divides into a lateral mesonephric fold and a medial genital fold. The lateral fold eventually includes the Müllerian duct, Wolffian duct, and the mesonephros, precursors of the uterine and urinary tracts. The median fold eventually contains the ovary.

Müllerian ducts are first identified in the urogenital folds in close relationship to the Wolffian ducts during the sixth week of embryonic life. By the fourteenth week these two ducts approach one another below the insertion of the inguinal ligament into the folds. Eventually the lower portions fuse to make a single median canal which later forms the epithelial lining of the uterus, cervix, and vagina.

Bilateral or unilateral failure of development may occur from six to ten weeks after conception. Arrested development on one or both sides during the

next four weeks may result in formation of a unilateral or bilateral rudimentary horn or in formation of the bicornuate type of uterus. After this time, failure of development may result in a septate type of uterus.

The actual cause of these failures of development is unknown. Felix and Anderson<sup>1</sup> have suggested that the left Müllerian duct advanced slightly ahead of the right and, on that basis, an error in timing during embryonic development would result. Curtis<sup>2</sup> and others have suggested that defective germ plasm and unfavorable embryonic environment were the most important factors. DeLee,<sup>3</sup> Miller,<sup>4</sup> and Jarcho<sup>5</sup> were inclined to the less complicated view, suggesting that the abnormalities were due to lack of fusion in whole or in part of the Müllerian ducts.

### Classification of Uterine Anomalies

Numerous systems of classification have been proposed and they have created much confusion. Kaufman divided uterine anomalies into four basic groups, each of which had several subgroups. These basic groups have had influence on subsequent classifications and consequently they are worthy of mention: (1) malformations due to faulty juxtaposition of the Müllerian ducts; (2) malformations due to faulty absorption of septa; (3) malformations due to aplasia; (4) malformations due to hypoplasia.

Since this basic grouping was published, many authors have listed different forms of various lengths and descriptions. However, the more recent articles have used the classification proposed by Jarcho<sup>5</sup> with slight modification in some instances. This particular proposal suggests seven basic forms and these appear to cover most of the abnormalities. In addition, it is most adequate for clinical grouping.

TABLE I. JARCHO CLASSIFICATION

UTERUS SIMPLEX (Normal)
1. Uterus didelphys bicollis (Septate vagina)
2. Uterus duplex bicollis (Vagina simplex)
3. Uterus bicornis unicollis (Vagina simplex)
4. Uterus septus (Complete)
5. Uterus subseptus (Partial)
6. Uterus arcuatus (Concave fundus)
7. Uterus unicornis

It is not our intention to attempt a review of the literature or to survey the vast problem of congenital abnormalities. We would rather take one interesting phase of the problem. This is relative to pregnancy in those patients who have been proved to have congenital anomalies of the uterus. Recent articles have shown a wide discrepancy of incidence and of observation for diagnosis, especially in those instances relative to pregnancy. There is also a variation in listed complications and in the management of individuals who experience these difficulties.

Our study concerns patients admitted to the Royal Victoria Montreal Maternity Hospital during the years of 1942 to 1953, inclusive. All cases included in this series were consecutive admissions either to the obstetrical wards

or to a gynecological service, with a definite diagnosis of pregnancy having been made prior to admission.

### Incidence

There were 39,190 admissions with a definite diagnosis of pregnancy during this twelve-year period. In this group there were 41 patients in whom a definite congenital abnormality was found. There were 56 pregnancies in this group. Some of these pregnancies occurred between the years of 1933 and 1942. For this reason only an approximate incidence of occurrence is attempted. This is estimated at 1 such anomaly in 954 of our obstetrical admissions. In addition, no cases of arcuate uterus were available from our index. This is due to the fact that we consider this condition common and thus it is not specially indexed. The eight cases of arcuate uterus which we have listed were selected from indexed abnormal presentations and difficult deliveries where this type of uterus was described in the case report. In every instance the condition was pronounced and the delivery was complicated by the presence of this phenomenon.

The various types which we encountered are listed in Table II.

TABLE II. INCIDENCE OF TYPES (JARCHO CLASSIFICATION)

1. Uterus didelphys	5
2. Uterus duplex	0
3. Uterus bicornis	20
4. Uterus septus (complete)	2
5. Uterus subseptus	5
6. Uterus arcuatus	8
7. Uterus unicornis	1
Total	41

TABLE III. TIME OF DIAGNOSIS OF ANOMALY

Routine physical examination		9
Uterus didelphys	3	
Uterus bicornis	2	
Uterus septus (complete)	2	
Uterus arcuatus	2	
Investigation for sterility (hystero-graphy)		2
Uterus didelphys	1	
Uterus bicornis	1	
Curettage or examination under anesthetic		6
Uterus bicornis	3	
Uterus septus (complete)	1	
Uterus subseptus	2	
Time of delivery		20
Uterus bicornis	11	
Uterus subseptus	3	
Uterus arcuatus	6	
Laparotomy for other conditions (fibroid, appendix, ectopic pregnancy)		4
Uterus didelphys	2	
Uterus subseptus	1	
Uterus unicornis	1	
Total		41

### Diagnosis

Fenton and Singh<sup>6</sup> state that with the exception of the septate types, diagnosis of congenital uterine abnormalities presents little problem. Many



have emphasized the importance of clinical manifestations as an aid in diagnosis. Miller<sup>4</sup> has drawn attention to menstrual upsets such as unilateral dysmenorrhea or abnormal types of menorrhagia being associated with these anomalies. Probably the most common lead to diagnosis is the frequent bleeding which occurs in the first trimester of pregnancy. This occurred in over 50 per cent of all our reported cases.

In spite of the statements by others we frankly admit that the majority of our cases were not diagnosed at the time of the original examination. This was the case in those individuals who were examined by us even before pregnancy occurred as well as in those who had their initial examination during the first trimester of pregnancy. It was usually when some incident necessitated special examination that the eventual diagnosis of this condition was established.

Undoubtedly some of the anomalies should be diagnosed without difficulty. This is provided the examination is not hurried and it is complete. Nevertheless, the various records have been examined in detail with reference to types diagnosed and when the diagnosis was first listed.

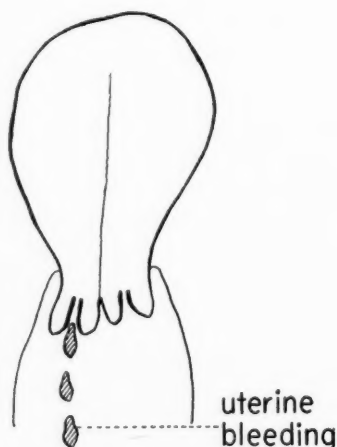


Fig. 1.—Case 1. Examination under anesthetic demonstrated these findings. The patient was approximately seven weeks pregnant and the uterus was slightly heart shaped. There was frank bleeding from the right cervical canal. It was erroneously thought that this bleeding was from the nonpregnant uterus.

### Pregnancy

With reference to fertility we cannot make any authoritative statement. In our small series there did not appear to be any appreciable diminution. It should be stated that no patient in this series experienced more than 3 pregnancies.

The coauthor has carefully reviewed every case and he has checked the records of other pregnancies which occurred in these individuals. There were only four cases in which the reports were not available. In these instances the history was obtained from the doctor or patient. In the 41 patients there occurred 56 pregnancies.

### Accidents Before Viability

Authorities (7) are constant in reporting an increased incidence of abortion associated with these abnormalities. In this regard figures vary from 27 to 53 per cent. Our results are given in Table IV.

TABLE IV. ACCIDENTS BEFORE VIABILITY

Total number of pregnancies		56
<i>Accidents before 12 weeks:</i>		
Abortion (spontaneous)	9	
Ruptured ectopic pregnancy	2	
<i>Accidents between 12 and 28 weeks:</i>		
Spontaneous labor	5	
		16 (28.6%)
<i>Abortion relative to anomaly:</i>		
Uterus didelphys	1	
Uterus bicornis	6	
Uterus septus (complete)	1	
Uterus subseptus	6	
Ectopic (didelphic 1, bicornuate 1)	2	
Total		16

### Premature Delivery

There is a paucity of material regarding the incidence of this complication. Many statements have been made creating an impression that premature labor occurs frequently. There are, however, few figures to substantiate these statements.



Fig. 2.—Case 1. The uterus is shown at the time of cesarean operation after removal of a living baby and the placenta. Note that the incision was made close and parallel to the thick septum which completely separated the two uterine cavities. The complete pregnancy was contained in the right uterus and the placenta was removed from the lower segment where there was a partial separation of implantation from the septum which caused the persistent antepartum bleeding. Note the irregularity caused by the nonpregnant uterus with the insertion of the Fallopian tube at a much lower level on the left side.

Our series of premature deliveries includes one cesarean section for hemorrhage from abruptio placentae and only 4 other cases in which the membranes ruptured or labor began spontaneously between the twenty-ninth and thirty-sixth weeks of pregnancy. All babies were liveborn, weighing 1,130, 1,320, 1,480, 1,780, and 1,910 grams. The smallest baby died a few hours after birth from

prematurity and intracranial hemorrhage due to active breech extraction for transverse presentation. The incidence of premature deliveries of viable infants in this small series is figured at 10 per cent.

There were no other major complications of pregnancy except in 3 patients who developed moderate pre-eclamptic toxemia. These individuals were treated in the routine manner and this condition did not influence the result. No cases of twins occurred in the series. There were 3 instances of moderate antepartum bleeding, 2 from partial abruptio placentae and one from placenta previa lateralis.

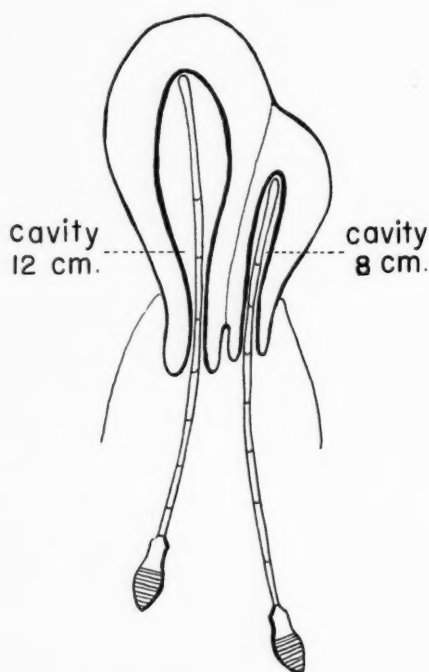


Fig. 3.—Case 1. Postpartum examination on the eighth day demonstrated lochial discharge from both cervical openings. With the use of pliable sounds, no communication could be found between the two cavities. The right cavity still was much more spacious than the left.

CASE 1 (Uterus septus, complete).—This case demonstrates many features which warrant emphasis relative to congenital anomalies of the uterus.

Mrs. B., aged 28 years and married six months, first consulted the doctor Jan. 22, 1953. Her history included marked dysmenorrhea preceding each menstrual flow; the chief symptom was persistent dyspareunia. A septate vagina, double cervix and uterus were diagnosed and she was admitted to the hospital where the vaginal septum was removed. Her next admission was on May 14, 1953, when she was seven weeks pregnant and was having pronounced painless vaginal bleeding. The Aschheim test was positive and pregnanediol levels were normal. Bleeding continued for one week and it was thought to be from the nonpregnant right uterus (this was proved to be erroneous at time of delivery). Bleeding ceased after ten days and the patient was discharged. Painless bleeding recurred on Nov. 29, 1953, two weeks before term. This bleeding persisted for 18 hours and thus influenced her doctor to perform a cesarean section. The pregnancy was in the right uterus and the bleeding was found to be caused by a low-lying placenta, a portion of which had separated from the medial septum. Figs. 1, 2, and 3, demonstrate findings at interesting occasions of observation.

### Labor

A high incidence of complicated labor is to be expected with uterine abnormalities.<sup>7</sup> We did not observe any increase of bony pelvic contraction; this occurred in only 3 patients. Abnormalities of lie and presentation were the chief complicating factors. Way<sup>8</sup> has drawn attention to the arcuate uterus and uterus subseptus as causative factors in transverse lie. Falls<sup>9</sup> has reported a similar series with a high incidence of breech presentation and an accompanying high fetal mortality.

In our series of 56 pregnancies with 40 viable deliveries, normal presentation occurred in 33 instances. Breech presentation occurred 4 times and transverse lie on 3 occasions. These presentations were associated once with didelphic and bicornuate types, twice with arcuate uterus, and 3 times with uterus subseptus.

Uterine inertia occurred in 5 instances, once associated with uterus didelphys and the other 4 times with the arcuate type. Others<sup>6</sup> have emphasized that the arcuate uterus may give a poor type of labor and will frequently terminate in difficult delivery. In the 8 cases reported in this series, one labor ended with a difficult breech extraction and fetal death; another labor was complicated by marked inertia and the patient was delivered by cesarean section; the remaining 6 patients were delivered by means of difficult midforceps. Even when one considers that this is a selected group it should be realized that, in this type of case, muscle coordination is frequently lacking.

Cesarean section was performed 6 times (Table V), on 2 occasions upon the same person. This patient had an original ectopic pregnancy in the left horn of a bicornuate uterus. All mothers and babies survived.

TABLE V. CESAREAN DELIVERY.

CASES	TYPE OF UTERUS	PRESENTATION	INDICATION	WEIGHT OF FETUS (GRAMS)
1.	Bicornuate	Transverse }	Previous ectopic pregnancy	3,270
	Bicornuate	Transverse }		3,540
2.	Bicornuate	Vertex	Partial abruptio	1,480
3.	Bicornuate	Breech	Android pelvis	3,190
4.	Uterus septus (complete)	Vertex	Low implantation (partial abruptio)	3,250
5.	Arcuate	Vertex	Marked inertia (moderate android pelvis)	2,750

While postpartum hemorrhage has been reported<sup>9</sup> to be frequent in these cases of anomalies, our records showed only two cases where the blood loss exceeded 500 c.c. One patient had antepartum bleeding due to partial separation of the placenta; the other delivery was complicated by a retained placenta which necessitated manual removal. In neither of these cases was the blood loss greater than 700 c.c. and transfusion of 500 c.c. in each instance appeared adequate.

Many authors<sup>6, 7</sup> have remarked upon the high incidence of retained placenta and the necessity for manual removal. Hunter<sup>10</sup> has given the incidence as



11 per cent. He has suggested that the nonpregnant uterus or horn, acting similarly to a full bladder, prevents the uterus from contracting.

It is our custom to remove the placenta manually only when there is definite delay in normal separation or expulsion. In our general obstetrical service the incidence of manual removal is less than 3 per cent. In the 40 deliveries of viable babies, manual removal was necessary on 8 occasions, an incidence of 20 per cent. The time interval ranged from 30 to 90 minutes following delivery of the baby. In several instances it was during this post-partum intrauterine examination that the congenital abnormality was first discovered.

### Results

There were no maternal deaths and no patient suffered from any permanent disability.

No congenital abnormalities were noted in the babies. Two fetal deaths occurred. One infant was premature, born by breech extraction in a patient with a uterus subseptus. The other was a full-term infant in a case of inertia of labor which was terminated by a difficult midforceps delivery. The mother had an arcuate type of uterus. The uncorrected fetal mortality of all viable infants, including deaths ante partum, stillbirths, and neonatal deaths, is 5 per cent.

There is no doubt that the babies are generally smaller even when there is certainty that the pregnancy progressed to full term.<sup>6</sup> Table VI shows that approximately 50 per cent of the infants weighed under 3,000 grams at birth.

TABLE VI. WEIGHTS OF VIABLE INFANTS

Over 3,500 grams	6
Between 3,000 and 3,500 grams	15
Between 2,500 and 3,000 grams	12*
Between 2,000 and 2,500 grams	1
Between 1,500 and 2,000 grams	3*
Between 1,000 and 1,500 grams	3
Total	40

\*Fetal death, intra partum 1, post partum 1. Infants discharged alive and well, 38.

Mention was made of the embryological development of the genital tract and the close relationship with that of the urinary tract. Collins,<sup>11</sup> Wharton,<sup>12</sup> and Woolf and Allen<sup>13</sup> have described these findings in detail. It is with regret that we state there were only 6 patients who had an adequate urinary tract investigation. There were 4 of these 6 patients who showed gross urinary tract anomalies in association with those occurring in the genital tract.

### Conclusions

1. Diagnosis is facilitated by inquiry relative to menstrual disorders, adequate examination of the patient, and bleeding in the first trimester of pregnancy.

2. Hemorrhage and onset of labor before viability are the greatest factors in fetal loss.

3. Abnormality of presentation and inertia during labor are hazardous. Cesarean section should be considered in these instances.

4. Operative interference with labor which is progressing normally is a common fault which causes unwarranted fetal mortality.

5. Adherent or retained placenta indicates manual removal.

6. Fifty-six pregnancies associated with congenital anomalies of the uterus are reported.

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## ENDOMETRIAL HYPERPLASIA IN RELATION TO GENITAL FUNCTION

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ENDOMETRIAL hyperplasia has been studied in various countries. Aside from Germany, the United States and Sweden have contributed most. Novak<sup>14, 15</sup> presented an excellent review of his observations. Kottmeier<sup>11</sup> published a monograph on this subject, and Taylor,<sup>23</sup> using convincing material, clarified the important question of whether cancer of the uterine corpus may originate from hyperplasia. Tietze,<sup>24</sup> Gruner,<sup>5</sup> Winter,<sup>28, 29</sup> Kyank,<sup>9, 10</sup> and Behrens<sup>2, 3</sup> added important contributions to the fundamental and special problems of hyperplasia, using the material from my department in Kiel and later from my department in Leipzig. It may seem unnecessary to report again on this topic. However, I believe a report on consistent observations through forty years will at least establish the reliability of certain general statements and give some clinical indications.

A complete discussion of the literature will soon be presented in a new monograph by my associate, Dr. Behrens. A short review may now show the way in which the concept of hyperplasia has become crystallized and sharply defined.

Since 1911, I have examined the pathological specimens from all operations of the gynecological departments of the university hospitals in Rostock (until 1922), Kiel (until 1936), and Leipzig (from 1936 to date). The entire anatomical material was freshly fixed and was examined either completely by myself or in cooperation with my associates. Obviously, there were endometria from hysterectomies as well as from curettages. This anatomical material was of great value as in each case the relevant clinical data and menstrual history were also available. In many cases we could examine both ovaries at the same time. Based on the combination of good menstrual histories and anatomical reports, our first studies in 1911-1912 immediately confirmed Hitschmann and Adler's findings on the cyclic changes of the endometrium. A new observation, however, was the distinction between a nonchangeable, basal part of the endometrium (basal layer) and a functioning stratum which displayed cyclic changes (functioning layer). In 1912-1913 we found the actual relationship by comparing the functional stages of the ovaries—follicle and corpus luteum—with the respective functional stages of the endometrium. Our findings on the corpus luteum, its origin from the granulosa layer of the follicle, and its vascularization by capillaries from the

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theca confirmed and completed the results of other authors as, for example, Robert Meyer. Soon it was possible to estimate the exact age of the corpus luteum within three days. By 1913 we had collected enough material to be able to describe the anatomical processes accompanying menstruation: the regression of the corpus luteum, the disintegration of the functioning layer, first superficially and later as far as the basal layer, the diffuse leukocytosis which is the first sign of the degenerative process, and, finally, the sequestration of some firmer remnants, and the re-epithelization of the entire wound originating from the basal layer. In this way, a basis for the clinical signs of the menstrual period was found and the time of ovulation could be clarified.

In the course of time, our studies showed more and more clearly that endometria occurred which did not fit into the picture of cyclic variation and which presented particular characteristic features. It was easy to separate the definite inflammations which were characterized in one group only by perivascular and periglandular infiltrations in both layers and in another by a diffuse, intense infiltration of the functioning layer which caused a suppression of the cyclic changes. The further course in such cases proved that the endometrium had a marked tendency to heal. The special conditions in miliary, ulcerous, or diffuse tuberculosis of the endometrium were elucidated and described. Further, we described the mechanical effects of fibroids on the endometrium, as, for instance, flattening over a fibroid which grows into the submucosa, or angular compression between two neighboring nodules. The course of the cycle was not influenced by these changes.

In the basal layer we frequently saw circumscribed adenomas characterized by a dense stroma with groups of firm arterioles and small arteries. These consisted chiefly of narrow glands with irregular course lined by cuboidal epithelial cells with dark nuclei. Not infrequently these adenomas protruded into the functional layer influencing its structure. In many cases the functional layer was wrapped about the basal adenoma like a coat; in some cases, however, it retained only at the sides a certain thickness and was flattened in the middle where it sometimes was represented only by a single row of cells. In exceptional cases, these adenomas display cyclical changes. Their importance lies in the fact that they are not shed during menstruation and therefore may cause localized disorders of desquamation and clinically lead to postmenstrual bleeding due to a retardation of wound healing over these circumscribed growths. If they are removed during curettage, they may cause diagnostic difficulties for inexperienced observers. As a rule, one finds typical cyclic stages in addition to such pieces of adenoma. Such nodules do not constitute a functional hyperplasia, but they are independently growing adenomas. They are slowly pressed toward the cavity and appear finally as polyps of the corpus.

All the previously mentioned groups fit into the normal cycle; even independent adenomas are present. They are consistent with the clinical signs, in particular with the history of bleeding. They always permit the conclusion



that a cyclic, biphasic ovarian process is occurring which influences the functional layer of the endometrium in preparation for the implantation of the fertilized ovum.

### General Anomalies of Amount and Interval of Menstruation

This knowledge was very useful for the clinical understanding of the so-called "gynecological bleeding." As long as no other factors are found, periodic bleeding is caused by a biphasic ovarian cycle and by the wound remaining after the shedding of the functional layer. The intensity of bleeding depends on the contractility of the uterine muscle; its duration depends on the healing time of the endometrial wound. *Excessive bleeding which, however, is limited to six to seven days* may be explained by adhesions, old parametritic processes, fibroids, relaxation of the muscle with lack of turgescence, hypoplastic myometrium, hypertension, or permanent venous congestion in the pelvis. In bleeding of more than seven days or in intermenstrual bleeding, we have to assume a *second* wound or another source of bleeding, as, e.g., ulceration of the endometrium in severe endometritis, erosion of the cervix, ectropion of the cervix with inflammation, vaginitis, polyps of the cervix or the corpus, cancer of the genital tract, etc. This is an example of noncyclical bleeding.

The duration of the interval between menstrual periods depends on the time the follicle takes for complete maturation to ovulation and on the time the corpus luteum remains functioning. *Anomalies of the interval* arise in the ovary and are due to the various factors influencing its function.

A clinical aid in diagnosis is the basal temperature which helps to estimate the time of ovulation. Further facts of diagnostic value are the condition of the vaginal epithelium and the morphology of the crystallization in the cervical mucus (although this has recently been questioned), the midcycle pain, and in well-equipped laboratories the demonstration of pregnandiol and perhaps of anterior pituitary hormone in the urine.

### Endometrial Hyperplasia

After exclusion of all these types of disorders, there still remained a rather large group of cases which were characterized by signs of hyperplasia. This group of cases had been known for a considerable length of time and had been assigned various names, such as chronic hypertrophic and hyperplastic endometritis (Ruge, Gebhardt), endometritis fungosa (Brennecke-Olshausen), stationary hyperplasia (Albrecht). Various types of the so-called bleeding uteri had also been called hemorrhagic metropathy by Aschoff and Pankow. All these names have become redundant and their use causes confusion since further experience and critical work-up of an ever growing material have made it possible to crystallize as a characteristic clinical picture the glandular or glandular-cystic *endometrial hyperplasia* due to a persistent action of follicular hormone (1914-1915).

This description is based on my material gathered in Leipzig from Jan. 1, 1937, to Dec. 31, 1952. We have collected in this time 49,870 anatomical specimens. Among these there are 3,295 certain cases of endometrial hyperplasia, that is, 6.6 per cent of a large clinical material. The results are comparable with those from Kiel and Rostock.

### Morphology of the Endometrium in Hyperplasia

The characteristic trait of *endometrial hyperplasia* is the fact that the endometrium does not correspond anatomically to any of the stages of the cycle. It presents signs of abnormally increased proliferation and it is usually impossible to differentiate between basal and functional layers. As a rule, the stroma shows in the deeper as well as in the superficial strata a narrow reticular structure; the cells are flat, spindle shaped, and have oblong, well-differentiated nuclei. Within the narrow stromal meshwork there are areas with loose structure and starlike cells connected to each other; the meshes contain fluid. Here and there in the stroma mitoses are to be found (cf. Novak). The vessels are straight without spirals. In the Bielschowsky stain the intercellular fibers are more numerous than in the simple proliferative phase. There are no decidua-like stromal cells with abundant plasma as seen at the end of the secretory phase. It is striking that foci of round cells or leukocytes are rare or missing. In a single case we found a few miliary tuberculous nodules in a hyperplastic mucosa.

The condition of the glands is very important for correct diagnosis. Their form varies greatly; there are straight glands, tortuous ones, glands with unequal lumen, and cystic ones—various shapes without a uniform rule. If the cystically widened glands are prevailing, we speak according to Novak's correct designation of a "Swiss-cheese type." Aside from the shape of the glands, the epithelium is the most important factor for the diagnosis. It has proliferative character, the cell plasma is acidophilic and the nuclei are oblong-oval and easily distinguishable. The cells are arranged in two or three dense rows and contain mitoses here and there. It is obvious that they are subjected to a considerable growth stimulus which, however, is not always manifested to mechanical reasons. This explains the varying shape of the glands and their cystic dilatation. Complete endometria from hysterectomies show that the endometrial thickness varies to a high degree. There are hyperplastic endometria which are 10 to 12 mm. thick, which is more than the thickest premenstrual functionalis.

There are, however, others that are not thicker than 3 to 4 mm. in spite of their clearly increased proliferative character. The surface is often uneven, protruding and even polypoid areas alternating with smooth or retracted ones. An intact surface in such an abnormally proliferative functioning layer is to be seen only as a secondary finding, for example, in a fibroid uterus or in a specimen from a hysterectomy for cancer of the cervix. This is the first stage of hyperplasia which has not yet caused functional clinical

symptoms, but it is usually found when the history would lead us to expect a secretory phase, that is, in the third or fourth week after the last, hitherto regular, four-weekly menstrual period. These cases certainly characterize the beginning of the process, but are rarely observed anatomically.

In the great majority of cases the abnormally proliferated endometrium is not found intact, but permeated with smaller or larger reddish patches. Histologically these patches correspond to thrombotic foci of necrotic disintegration. They may be so small that they can be found only by means of a series of slides, but usually they are immediately recognizable, and sometimes they are so outstanding that bloody shreds hang down into the cervix from scarcely intact, pale parts of the endometrium. Tietze found these thromboses and necroses 87 times among 100 systematically examined cases. In the remaining 13 cases it was possible that these parts were lost in the process of embedding the material from curettage. It is remarkable that few of any histological signs of demarcation are visible at the border of necrotic and the still intact proliferative tissue; but it is still determinable that the border is very sharp.

Finally, there are other uteri where the entire cavity of the corpus constitutes an irregularly nodular wound surface. Histologically one sees only areas of the basal layer with mostly narrow glands. The superficial epithelium is replaced by a layer of fibrin, cellular detritus, and blood. This is Kottmeier's "burnt out" hyperplasia. From here the basal layer regenerates by epithelization and is ready for new transformations.

### **The Ovary in Endometrial Hyperplasia**

What is the ovary like in such cases of endometrial hyperplasia? Obviously, it is only rarely possible to obtain the uterus and both ovaries. However, from recent years I possess 34 pairs of ovaries in cases of endometrial hyperplasia. In those ovaries we found large and small follicles; the larger ones presented a well-defined internal theca; in some of them the granulosa was well preserved and had six, eight, or twelve layers. Once we found an intact, 120 micron large ovum in a normal cumulus oophorus. This follicle had a diameter of almost 20 mm. In others we found only remnants of granulosa. However, in cutting out the follicle, the granulosa which is only loosely connected with the basement membrane is easily detached and may be lost in the further handling of the preparation. The condition of the theca interna informs experienced observers as to the real state of things.

Other ovaries presented follicles with beginning atresia and only small remnants of granulosa and a well-defined, already hyalinizing basement membrane; the adventitial cells of the internal theca are hypertrophic and show fat infiltration. In such cases the follicle must, therefore, have been functioning shortly before. If one desires to judge the exact quantity of follicular hormone-producing tissue, one has to dissect the ovary into 1 to 2 mm. thick disks and cut many slides of each such disk and count the follicles. In some

cases worked up in this manner, we always found well-functioning estrogen-producing tissue.

Another finding was equally important. There was never a functioning corpus luteum, and the last which had functioned was at least six to eight weeks old, which means it was just still visible. From these findings we may draw the obvious conclusion that the last biphasic cycle was terminated by bleeding four to six weeks or more earlier, and that since that time only follicular action was present. This means that the follicular hormone continued acting after the follicular phase and that its effect persisted. We spoke of "follicular persistence" (1915). This does not necessarily mean that only a single follicle persists and functions three to four weeks beyond the usual time. It may happen that a mature follicle functions for some time, then becomes atretic and is replaced by a second or third one. The important fact is the persistent hormonal action.

The correctness of this conception is proved by the administration of follicular hormone preparations to women whose ovaries no longer function or have been removed or inactivated by x-rays. Depending upon the sensitivity of the patient, various doses of follicular hormone may produce genital bleeding necessitating curettage because of the possibility that a cancer of the corpus may be present. Such a curettage usually reveals an endometrial hyperplasia. In women without ovaries and with normal sensitivity one may build up a normal proliferative phase with 5 doses of 5 mg. estradiol benzoate or similar preparations of follicular hormone. With 10 doses of 5 mg. of the hormone one may produce hyperplasia.

Another source of follicular hormone is the hormone-producing ovarian tumors (see Novak,<sup>15</sup> Kottmeier,<sup>11</sup> Huber,<sup>7</sup> Limburg,<sup>12</sup> Kyank,<sup>9, 10</sup> Behrens<sup>2, 3</sup>), namely, the granulosa-cell and theca-cell tumors. In agreement with Kottmeier, I am convinced that the theca-cell tumors are granulosa-cell tumors with connective tissue organization. I believe that I can prove this on the basis of many examples of transitions between both types. These tumors with hormonal action need not be palpable, for we have described nine cherry-sized and small walnut-sized granulosa-cell tumors which had the same effect as large ones (Kyank, Behrens).

All these observations clearly show that persistent and perhaps also excessive action of follicular hormone is found associated with endometrial hyperplasia. Admittedly, there occur very rare cases of definite endometrial hyperplasia where none of the above-mentioned three sources is demonstrable. In my material collected over 40 years I have only two such cases. Both women had been in the menopause for many years and were over 60 years of age. The question arises whether the adrenals are able to produce a folliculin-like hormone in sufficient quantities to cause a hyperplasia, or whether hypertrophic cells near the ovarian hilum are the source of this hormone (Husslein<sup>8</sup>). Morató Manaro<sup>13</sup> (Montevideo) states that he has produced endometrial hyperplasia in guinea pigs with extracts of suprarenal cortex or with Percorten (Montevideo, 1940).



The pathogenesis of endometrial hyperplasia appears from the picture of the ovaries and the endometrium, to be ascribable, in all probability, to the follicular hormonal action which persists over a long time or is excessive. This effect is the same as in the follicular phase of the bi-phasic cycle, but intensified and prolonged. Its effect though of the same quality as that productive of the normal proliferative phase is longer lasting and more intense and hence produces an excessive, irregular proliferation.

This intense and pathologically increased endometrial proliferation includes the germ of its own destruction. As soon as the production of folliculin diminishes, the stimulation for proliferation stops; the overgrown endometrium degenerates, "fades," or "withers." The irregular circulation stagnates. Hemostasis and necrosis lead to localized disintegration which may be, depending upon a failure or repetition of the follicular stimulation, temporary, limited, and reversible, or else it proceeds slowly until the entire endometrium is destroyed.

#### **Differential Histological Diagnosis and Special Forms of Hyperplasia**

Before discussing the clinical picture of the endometrial hyperplasia, some considerations regarding the differential diagnosis have to be mentioned. Is the endometrial hyperplasia always clearly recognizable in the microscopic slide? This question may be answered in the affirmative if one carefully observes the previously described signs.

One must be familiar with the changes of the normal endometrium during the cycle. In recent years we have given our special attention to variations of the morphology of the normal cycle. We found that in addition to a certain average picture, there occur numerous deviations. With regard to the phase of the cycle, the basal layer presents varying thickness in relation to the functionalis. The boundaries of the basal layer from the functioning one and from the muscle are even, even disregarding the endometrial folds.

The adenomas and the difficulties they cause for the diagnosis based upon curettings were mentioned above. The participation of the basal layer in the cyclic changes varies a great deal. Often it does not participate in the secretory phase at all, often it is completely included. The border line between basal and functioning layer lies in the area of the basal vessels which are clearly to be distinguished and constitute the origin of the vessels for the functioning layer.

In the premenstrual phase the functioning layer is usually 4 to 5 mm. thick; at the end of the second week, still during proliferation, its thickness is at least 3 mm. It happens sometimes, however, that these dimensions are not reached, that the functioning layer is poorly developed and even shortly before menstruation may not be thicker than  $1\frac{1}{2}$  to 2 mm.

For the differential diagnosis of hyperplasia it is of great importance to remember that the endometrium of the proliferative phase on the twelfth or thirteenth day after the onset of bleeding may already be 5 mm. thick with straight glands whose epithelial cells are arranged in a single row and whose

stroma is loose and delicate. Mitoses are easily visible at this time. Such an intense proliferation is a normal manifestation of the cycle and not a hyperplasia in the sense previously defined. In the premenstrual phase the functioning layer may be 10 mm. thick or even more and may be irregular. It displays, however, in the stroma as well as in the glands only the signs of the secretory phase. During the next days, in the course of regular menstruation it will be completely destroyed. It will be regenerated after healing of the wound, starting on the fourth or fifth day. This is not a hyperplasia, but merely a high, especially well-developed functioning cyclic mucosa.

The number of glands in the normal functional layer likewise varies to a high degree. There are mucous membranes with many and others with few glands and all transitional stages in between. Sometimes the basal layer appears to contain more glands than the functioning one. This, however, is probably only an illusion since the glands of the basal layer may be corkscrew shaped and may be cut several times in one cross section.

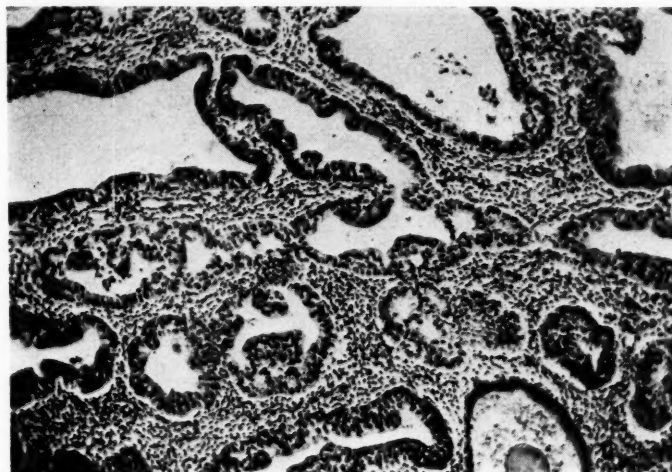


Fig. 1.—Glandular hyperplasia rich in glands. The 49-year-old patient remained healthy through five years. ( $\times 90$ .)

Finally, it has to be mentioned that the follicular and corpus luteum hormones usually act in an even manner on the entire endometrium of the corpus. However, in certain cases one sees that the glands in the areas of some small vessels lag behind in the change to the secretory phase. Obviously, the corpus luteum hormone has reached such areas in insufficient quantities. The most reliable sign is the condition of the epithelial cells and the observation of these rarely leads to mistakes.

As in the case of the cyclic endometrium, the hyperplastic one also displays certain variations from the typical course. We already mentioned that the proliferative development of the layers varies. The general histological picture, as seen in curettings as well as in complete endometria from hysterectomies, permits the differentiation of two forms: one with the emphasis on the stroma, the other a glandular or glandular-cystic type.

The *stromal* form presents large, dense fields of stromal cells. The glands are hyperplastic and show an irregular course, but remain in the background. The stromal cells, with large, oblong nuclei and slender cytoplasm, lie in dense rows. The vessels are not conspicuous. However, the picture is not compact throughout, for, especially under the surface, there are areas of loose tissue and infiltration of fluid. This variation occurs in approximately 5 per cent of cases.

Highly important are *deviations* in the *glandular picture*. Cases with remarkably few glands are harmless. They correspond to the mucosas poor in glands which we mentioned among the variations of the cyclic endometrium. In these cases the hyperplastic character is expressed by the bizarre, polymorphous shapes of the infrequent glands, and by the dense, far too numerous epithelial cells of proliferative character.



Fig. 2.—Glandular hyperplasia with intense, atypical epithelial proliferation. The 47-year-old patient has been under observation for 4½ years. She has been in the menopause for 6 months. (×170.)

Without clinical importance also are cases where the epithelial cells of the typically hyperplastic mucosa present, more or less clearly, signs of vacuolization similar to that seen in the normal secretory phase. Their distribution, however, is quite irregular. Twice we have had the opportunity of examining the ovaries in such a case, and found a fresh corpus luteum as the cause of the secretory signs. It must obviously happen that in spite of the long-lasting effect of follicular hormone, a persistent or another follicle ruptures and becomes a corpus luteum. Gruner could produce such effects with 200 to 400 mg. of corpus luteum hormone, though localized in larger or smaller areas and not in the entire mucosa.

Of special importance are the patterns with numerous glands of hyperplastic character. Such a picture develops in mucous membranes rich in glands. Often, the glands lie quite near to each other, with little stroma between them, and display numerous turgescient epithelial cells with mitoses.

Usually such rich glandular fields are not to be found in the entire mucous membrane. Typically between areas with a normal number of glands presenting all the signs of hyperplasia, there are others with collections of glands, mostly showing a narrow lumen. Thus the less experienced histologist gets the impression of an adenoma or even adenocarcinoma. In such conspicuous areas certain atypical findings may be present. Some glands may present distorted dilatations, others may display unusual destructive changes of the epithelial cells and the lumen may be filled with cell detritus. Diagnosis becomes more difficult when the epithelial cells in such dense glandular fields change their proliferative character. They may grow club-shaped bulges into the lumen, or form small, compact fields and seem to burst the basal membrane. The nuclei become larger and unequal, the plasma gets lighter, the cell shape and their connections become irregular. Sometimes light epithelial cells with small nuclei, similar to those of the high secretory phase, may develop in one or the other glandular tube. In others, the cells may be cuboidal and form areas similar to a squamous-cell epithelium. Photomicrographs demonstrate these phenomena better than a description (Figs. 1 to 5).

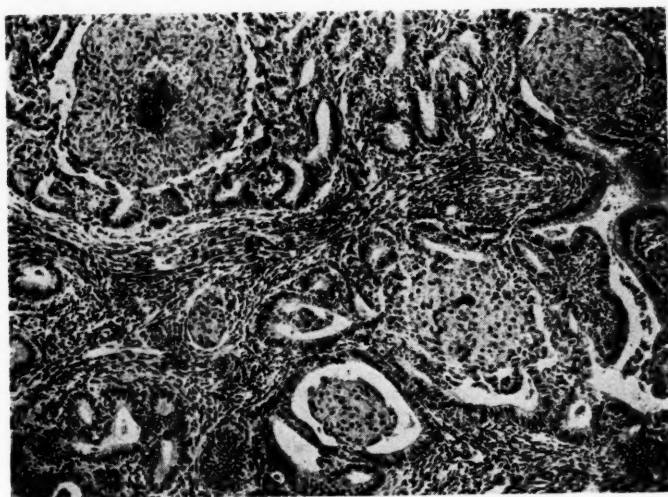


Fig. 3.—Patient 35 years old. Hyperplastic mucosa with numerous squamous epithelial cells. Curettage in 1941, since that time regular menstruation and a normal confinement. ( $\times 97$ .)

#### Relationship of Hyperplasia to Carcinoma

All authors engaged in serious studies of endometrial hyperplasia have described and illustrated these phenomena (Novak, Taylor, Kottmeier, Tietze, Gruner, Winter, Kyank, Behrens, and others). The patterns are very important since the decision as to "whether still benign or already malignant" is very difficult. Moreover, they are related to the question of whether an adenocarcinoma may develop on the basis of glandular hyperplasia and how great this danger may be. Only further careful observation of such patients in intervals of six to eight weeks will be able to decide these questions.

Our material up to 1930 was carefully examined in this respect by Tietze. The present discussion, however, is based on the material from Jan. 1, 1937, to



Dec. 31, 1952. Gruner, Winter, Kyank, and Behrens have reported in detail on this problem and Behrens has recently been working up the entire material in a monograph. I shall quote some of his figures: Among the aforementioned sum of 49,870 histologically examined cases from this period of time, there were, as mentioned above, 3,295 typical endometrial hyperplasias. Among these 3,295 patients there were six cases in which in the first preparation we found or at least strongly suspected, in addition to the glandular-cystic hyperplasia, a localized adenocarcinoma. Five of these cases were confirmed at the operation. The sixth patient was cured of her doubtful cancer by intracavitary radium therapy and has lived 11 years without recurrence. Aside

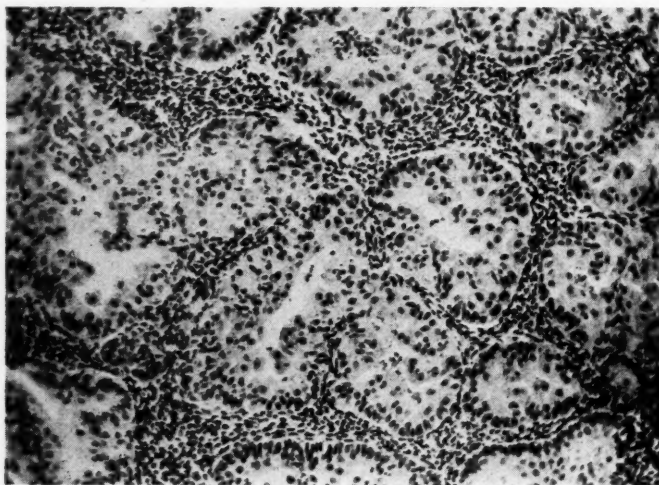


Fig. 4.—Glandular hyperplasia with intense epithelial proliferation. The 43-year-old patient has been under observation for 19 months. Eleven months ago x-ray castration; since that time no bleeding. ( $\times 170$ .)

from these six cases with five definite and one very probable malignancy, 47 other patients displayed the above-described accumulation of glands with or without atypical findings. That means that 1.4 per cent of the hyperplasias were suspected of a developing cancer. All these cases have been kept under careful clinical observation. Their histories of menstrual or abnormal bleeding have been reported in writing and the patients have been examined at regular intervals. In four of these 47 cases we found at subsequent curettage, performed after six, nine, twelve, and sixteen months, respectively, an adenocarcinoma. During the observation period following the first curettage, itself performed because of continuous bleeding, these patients had returned to a typical menstrual cycle of approximately four-week intervals and three days' duration. A renewal of the pattern of continuous bleeding was the reason for the second curettage which established the diagnosis of cancer. In three cases the adenocarcinoma was definitely proved in the removed uterus and in all of these it was localized in the tubal cornua. The fourth patient reported scant bleeding with long intervals between of many weeks' duration but this patient was an exception and did not report regularly to the clinic. After

twelve months a hysterectomy was performed and there was found a very immature, almost sarcoma-like cancer which filled the entire uterine cavity and had metastasized to the ovary and the omentum.

The other 43 patients of the total of 47 were observed for many months, some for several years, and they have remained well.

Based upon the observation that among 3,295 definite cases of hyperplasia a total of only 10 cancers of the uterine corpus have been observed, that is, 0.31 per cent, the conclusion must be reached that the danger of cancer development in hyperplasia is very small. On the other hand, the question arises whether we may decide from the fact that among 47 cases of excessive and often atypical hyperplasia four cancers were eventually established, that a cancer may

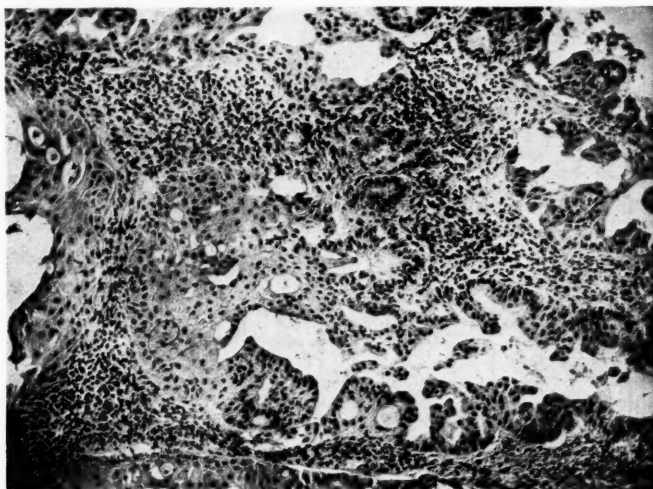


Fig. 5.—Intensely proliferated glandular epithelium in glandular hyperplasia. The 56-year-old patient has been under observation for 3 years. She is well. ( $\times 90$ .)

originate from such a hyperplasia. It is not possible to settle this question with certainty, but it does not seem probable. The reasons against this opinion are the following: In our cases the cancer was with one exception strictly localized and had probably required more than a few weeks for its development. The hyperplasia, on the other hand, is a functional anomaly, limited to a few weeks. Therefore, the cancer was probably present *before* the hyperplasia. Almost all the previously mentioned authors agree with this opinion.

A final reason would be the fact that only with excessively high doses of follicular hormones, doses which are never given in man, has it been possible to produce carcinoma-like reactions. However, it is noteworthy that approximately 1 to 2 per cent of the women with *atypical* hyperplasias react to follicular hormone, in which cases it makes no difference whether the sensitivity is extremely high or the hormonal secretion exceptionally strong.

We have to add a few words on the reaction of the other parts of the genital tract. The tubes present the characteristic picture of the late proliferative phase with the exceedingly dense, high, ciliated epithelial cells. The vagina is

in the stage of the proliferative phase with a prevalence of the acidophil, squamous epithelial cells with small, pyknotic nuclei. The muscles of the whole genital tract are well developed, well vascularized, and turgescient. While repeated episodes of persistence of follicular action, a uterus may develop a certain thickening of the muscle, formerly often called a "metritic" uterus.

### Clinical Aspects of Endometrial Hyperplasia

The age distribution (Fig. 6) is very remarkable. The incidence has remained unchanged without noticeable deviations through all the 40 years of observation. The last years of the reproductive period give rise to four-fifths of all cases; the first years of reproductivity, however, also show a small peak, while the time of puberty is hardly affected.

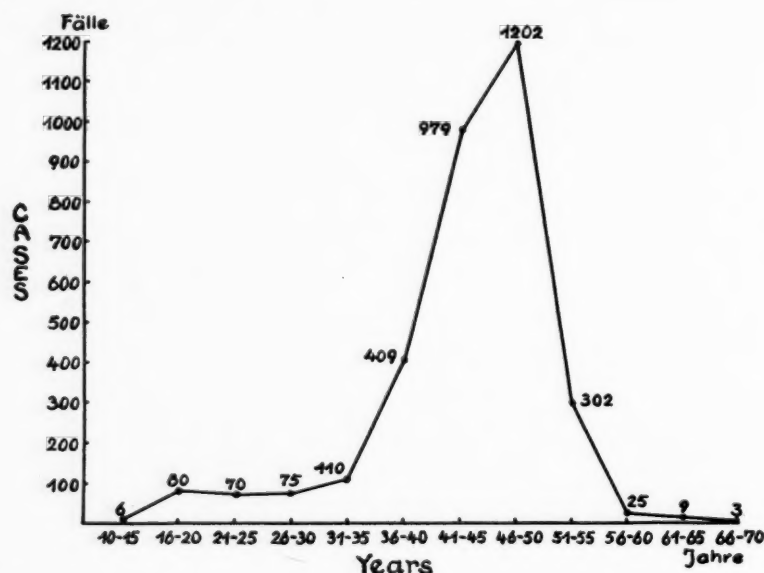


Fig. 6.—Age distribution of 3,270 cases of endometrial hyperplasia observed in the gynecological department of the University Hospital at Leipzig from 1937 to 1952.

Frequent relapses are characteristic. A certain cyclic character becomes evident since an amenorrheic phase accompanies the beginning of follicular stimulation during the abnormal build-up of the hyperplasia; a shorter or longer phase of bleeding follows; this cycle terminates with the complete necrosis of the hyperplastic mucosa and the following epithelization of the mucosal wound. The follicular stimulation increases until the onset of the bleeding; then it usually decreases if a new proliferating follicle does not substitute the one undergoing atretic degeneration. This is the picture of a monophasic cycle with protracted course and it is essentially analogous to the short monophasic cycle of the anovulatory bleeding.

The occurrence of such monophasic cycles at the beginning and end of the reproductive period, their combination with disorders of the intermenstrual interval, their onset at times of physically and psychically lowered resistance,

as, for instance, after confinements and/or a complicated puerperium, grave general injuries, and serious psychic strain permit the assumption of disorders of endocrine balance. Such an imbalance may be supposed to exist between ovaries, brain stem, and anterior pituitary lobe, or between the suprarenals and the thyroid gland. However, concerning this subject, we still have only vague hypotheses. We may only say with certainty that a local disorder of the ovarian tissue, such as the occasionally mentioned very firm albuginea, is not the primary cause.

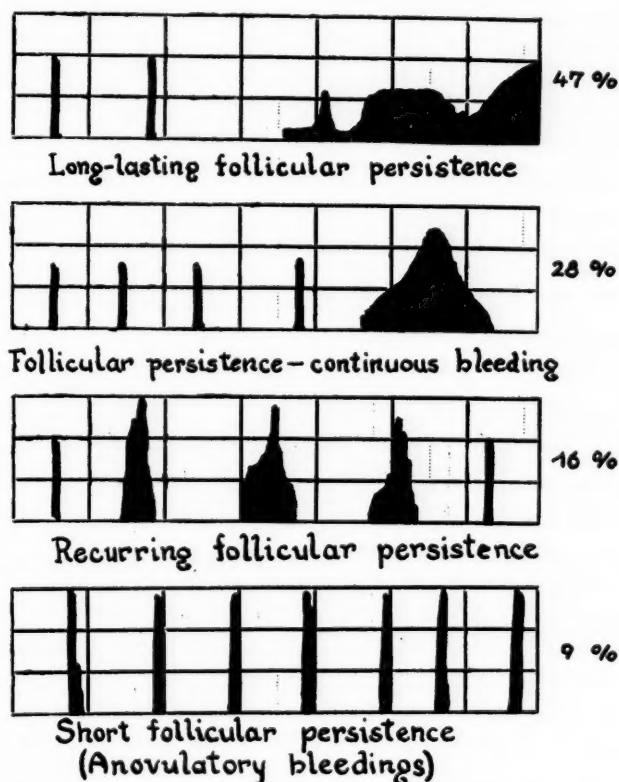


Fig. 7.—The types of bleeding in glandular hyperplasia in 1,165 cases from 1949 to 1952.

Married or unmarried women in the first and middle years of the reproductive age may develop, between series of quite normal cycles or between typical periods separated by shortened or prolonged intervals, hyperplasia with persistent follicles. This means that the patient has between biphasic cycles long-lasting monophasic ones with hyperplasia, just as anovulatory bleeding is sometimes interpolated between normal cycles. There are rare cases of women who during their entire lives have only a few biphasic cycles. During these short periods they are able to conceive; otherwise, they suffer from frequently recurring, continuous bleeding.

The course of these prolonged monophasic cycles is best recognized from the type of bleeding. Notwithstanding some other variations, they may be



grouped into the four general types illustrated in Fig. 7. As is obvious from the figure, the first three display continuous bleeding, while the last type only resembles menstruation and so approaches the anovulatory type.

As a rule, the intrapelvic examination does not reveal any anomaly. Hyperplasia may, however, accompany fibroids, ovarian tumors, anomalies of position, cancer of the cervix or the vagina. No sensations of the genital organs are observed. Occasionally increased libido is reported.

As a rule, the general health of the patient is not disturbed. In certain cases, however, a considerable degree of anemia may develop, which may progress into thrombopenic dyscrasia. It is remarkable that even profuse, continuous bleeding may often on the other hand cause a comparatively small change in the blood picture. In spite of the heavy and continuous loss of blood, the blood regeneration seems to proceed well, and may even be stimulated by the folliculin. Contrariwise, there are cases, especially in young persons, where comparatively small losses of blood cause very grave anemias. In such cases where the regeneration does not keep up with the loss, the general health may be seriously disturbed. Fortunately, such cases are rare.

#### **Treatment of Hyperplasia of the Endometrium**

The functional disorder in the menopausal women reacts comparatively well to treatment. The first step is the diagnosis, which is made probable by the type of bleeding but which has to be verified by examination of the endometrium from curettage. In 50 per cent of the cases the hyperplasia does not recur after curettage. What happens in the other 50 per cent?

As the loss of ovarian function is imminent anyway, an x-ray castration or the elimination of the source of bleeding by a radium insertion in the uterine cavity (100 mg. Ra  $\times$  20 hr.), or a vaginal hysterectomy may be indicated if recurrence or blood loss makes treatment necessary at all.

The treatment of preclimacteric cases, especially in young individuals, is very difficult. There is no definite routine for the therapy. In virgins, histological verification is not always necessary, since the diagnosis is at least very probable from the pattern of bleeding. Moreover, a cancer of the corpus is highly improbable in young women. Hormonal treatment, either with high doses, such as a single injection of 20 to 40 mg. of follicular hormone (the so-called "Entlösungseffekt"), or with high doses of progesterone, such as 60 mg. or more twice daily for five or six days or with male hormone (50 mg. testosterone on four successive days). All these methods are successful now and then, but are more frequently unsuccessful.

We must not forget that the prolonged monophasic cycle will stop some day by itself and then the bleeding ceases spontaneously. If there is no urgent indication, such as blood loss with increasing anemia, it is best not to do anything radical, but to wait with careful observation. If the bleeding increases, a cautious curettage of the functional layer alone is indicated. As far as possible, the basal layer ought to be maintained since it has various functions to fulfill. Such a curettage may be occasionally repeated to eliminate heavier loss of blood in obstinately recurring cases. Under such conditions, it is of paramount importance to win the full confidence of the patients in order to

help them effectively over these extremely uncomfortable disorders of the reproductive organs. Operative interference with the ovaries is useless even if a follicle grows somewhat larger than the average. Temporary radiation castration is to be avoided.

Quite successful sometimes is general improvement of the living conditions or change of climate for several months. Mountains of medium height are preferable; hospitalization is not necessary; even holding a job in a different climate is successful. In cases with severe blood loss blood transfusions are necessary. The treatment of the nonmenopausal endometrial hyperplasia due to excessively prolonged action of the follicular hormone requires consideration of all details and a very careful medical guidance of the patient.

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## ON THE MECHANISM OF UTERINE BLEEDING

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THE most notable characteristic of female genital function is menstruation, or cyclic uterine bleeding. Since ancient times this event has been associated with mysterious interpretations. The scientific basis for menstruation has been elucidated only during recent decades. Menstruation is a complex process initiated by the functional harmonious cooperation of the anterior pituitary lobe on the one hand and the ovarian hormones and the uterine mucosa on the other. We believe that the regulating factor of the entire cycle is the estrogenic hormone, the estrogenic hormone level operating similarly to the mercury level in the regulator of a thermostat whereby small doses of estrogen start the motor while large doses stop it. Which factors bring about the bleeding? That bleeding is not a prerequisite for the generative cycle and the implantation of the ovum is shown by the fact that most mammals undergo cyclic processes in the endometrium with proliferation and regression without bleeding. Cyclic bleeding occurs only in primates.

The interesting problem of the mechanism of bleeding has for many years occupied a number of outstanding investigators; various theories have been advanced but none of them has so far sufficiently clarified the mechanism of uterine bleeding. Most interesting are the estrogen-withdrawal theory of Allen<sup>1</sup> and the theory based on the vascular changes discovered by Markee,<sup>2</sup> Bartelmez,<sup>3</sup> and others.<sup>4, 5, 6</sup>

In former years it was believed that menstruation could be produced by progesterone only if the endometrium was previously brought to full proliferation by estradiol. We<sup>7</sup> were able to demonstrate in 1938 that this is not correct. We succeeded in producing "bleeding" not only by withdrawal of estrogen but also of progesterone. If a normally menstruating woman is given injections of 10 mg. of progesterone on five successive days during the intermenstruum, from the sixth to the tenth day, "bleeding" occurs after an interval of 48 hours (on the twelfth day). We referred to this as "intracyclic bleeding." In the same manner "bleeding" can be produced with progesterone in an amenorrheic woman (secondary amenorrhea) without earlier treatment with estrogens.\* Our<sup>8</sup> simplified method of treatment of amenorrhea with progesterone which induces bleeding after 2 injections of progesterone is based on the preceding observations. The bleeding issues from a thin mucosa in the proliferative phase.

\*Our findings concerning the induction of "bleeding" by means of progesterone were confirmed by P. Eckstein (J. Endocrinol. 6: 405, 1950) and P. L. Krohn (J. Endocrinol. 7: 318, 1951) in their experiments on monkeys (*Macaca mulatta*) in the laboratory of S. Zuckerman.

In women with secondary amenorrhea and hypoplastic uteri we<sup>7,8</sup> produced "bleeding" with progesterone three times in one month, the progesterone treatment being started each time two days after cessation of bleeding. To cite the following examples:

CASE 1.—K., aged 26 years, had been amenorrheic for seven years. The uterus was 4½ cm. long and narrow. She was given progesterone over a period of five days (50 mg.). "Bleeding" took place from the ninth to the twelfth day. After another course of progesterone had been given from the fourteenth to the eighteenth day, "bleeding" occurred on the twenty-second day and persisted up to the twenty-fifth day. After an interval of one day, a third course of treatment was given from the twenty-seventh to the thirty-first day, whereupon very copious "bleeding" occurred a third time on the thirty-fifth day and persisted up to the thirty-eighth day.

CASE 2.—K., aged 19 years, had been amenorrheic for a year. After five days' treatment with 50 mg. progesterone, bleeding set in on the eighth day and lasted until the eleventh day. The second course was given from the thirteenth to the seventeenth day and "bleeding" took place a second time from the twentieth to the twenty-third day. After having waited for one day, the third course of progesterone was given from the twenty-fifth to the twenty-ninth day, and on the thirty-second day bleeding occurred a third time and persisted up to the thirty-fifth day.

Endometrial biopsy at the beginning of the third bleeding revealed a very thin atrophic mucosa consisting only of the basal layer and several glands. This finding made it appear doubtful whether the explanation based upon alteration of the coiled arterioles could be applied to all cases of uterine bleeding. The specific mechanism of menstrual bleeding as described by Markee, the rapid regression of the endometrium and the resultant buckling of the coiled arterioles supplying the functionalis cannot take place in our cases because a functionalis is hardly present, i.e., the upper layers of the endometrium, where the coiled arterioles develop, are missing. Kaiser<sup>9</sup> denies that the increased coiling of the spiral arterioles of the superficial two-thirds of the endometrium is responsible for bringing about bleeding in the endometrium. He described the absence of such vessels from the endometrium of menstruating New World monkeys, and their almost complete absence from the endometrium of rhesus monkeys which had received massive doses of estrogens which induce withdrawal bleeding upon discontinuation. Kaiser believes that menstrual bleeding occurs whether coiled arterioles are complex, simple, or altogether absent. The main purpose of these vessels, he claims, is for the process of implantation of the embryo and not for the process of menstruation.

On the basis of his experiments on the exteriorized uterus (uteroabdominal fistulas) of the monkey (*Macaca mulatta*) Hisaw<sup>10</sup> also comes to the conclusion that the presence of coiled arterioles is not essential for menstruation and that ischemia is not a necessary prerequisite.

In recent years we have determined by endometrial biopsy that, among a thousand cases of functional bleeding in women, bleeding occurs from an atrophic endometrium in 5 per cent of the cases. In such an endometrium the development of the spiral arterioles can only be rudimentary or absent.

There is no doubt that after withdrawal of the hormone supply a bleeding can be produced in a castrated woman or monkey. The withdrawal theory of



Allen must, however, be extended to include the fact that not only the withdrawal of estrogenic hormone but also of progesterone will produce a bleeding. Furthermore, Krohn<sup>11</sup> was able to induce intermenstrual bleeding in normal rhesus monkeys with desoxycorticosterone (40 to 50 mg. DOCA), and at times with testosterone propionate as well, so that, according to Zuckerman,<sup>12</sup> any steroid with physiological action with the exception of the glucocorticoids can induce bleeding as a withdrawal effect in spayed monkeys.

In the following it will be shown that uterine bleeding may also take place with a constant hormone level, that is, without hormone withdrawal.

A. In women functional bleedings are known (*metropathia haemorrhagica*) caused by hyperestrinism resulting from a persistent follicle which at times can reach the size of a fist. We had the opportunity to perform laparotomies in such cases with special indications (myoma, etc.) at the beginning of the bleeding. The persistent follicle was found intact with an estrogen content of about 4 M.U. per cubic centimeter. The endometrium revealed glandular cystic hyperplasia and the quantitative determination of the estrogenic hormone in the urine failed to show any change as compared to the preceding days. Thus we have here a bleeding which occurs in hyperproliferated mucosa, without any change in hormone elimination—that is, a bleeding without hormone withdrawal.

B. For several years, we have been treating women suffering from primary amenorrhea or prolonged secondary amenorrhea with intravaginal implantation of estrogen pellets.<sup>13</sup> In these cases of amenorrhea there is no ovarian function. This can be recognized by the severe hypoplasia of the uterus, the resting endometrium, the absence of estrogen reaction in the cervical mucus and vaginal smear, and the reduced or totally absent excretion of estrogens. Several weeks after pellet implantation the effect of the estrogen action can be determined objectively, particularly by the growth of the uterus and the proliferation of the previously atrophic endometrium, the positive vaginal smear and abundant secretion of cervical mucus. Then suddenly a bleeding occurs, even though on the preceding day no change could be observed in estrogen excretion\* or in the secretion of cervical mucus. Shortly before the bleeding such mucus dried on a slide reveals the typical abundant crystal formation (arborization). At the onset of bleeding the biopsy shows a proliferated or usually hyperproliferated mucosa (glandular cystic hyperplasia). Thus we are here dealing with a bleeding from a hyperproliferated endometrium without any apparent withdrawal of the estrogenic growth stimulus.

C. Hisaw<sup>10</sup> made the following observations in his experiments with utero-abdominal fistulas: If a monkey is treated daily with 10  $\gamma$  estradiol, and 2  $\gamma$  progesterone are instilled on the twenty-third day into the lumen of the uterus, a bleeding occurs after 57 hours although the injections of estrogenic hormone were continued without interruption. The local application of 2  $\gamma$  of proges-

\*Thus, five months after implantation of a pellet containing 40 mg. of estradiol benzoate we observed 200 M.U. of estrogen in a 24-hour urine specimen, before as well as after the bleeding. We found 25  $\gamma$  estrone-estradiol and 66  $\gamma$  estriol per day determined fluorometrically by the method of Finkelstein. In a case of primary amenorrhea we found 6½ months after intravaginal implantation of 60 mg. of estradiol benzoate a total estrogen content of 330 M.U. per day in the urine (fluorometrically: estrone-estradiol, 30  $\gamma$ ). These values did not change either before or after the onset of the spontaneous bleeding.

terone (only a small part of which is absorbed by the endometrium) could certainly not have lowered the estrogen level in the blood, since the treatment with estrogens was maintained. This experiment also proves that endometrial bleeding can occur without hormonal withdrawal.

Must it be assumed that the estrogenic hormone acts as such or does it stimulate a bleeding-inducing substance in another gland? We<sup>14</sup> carried out experiments in the rabbit in which ovulation does not occur spontaneously but only after copulation, and in which the generative cycle takes place without bleeding. If 100 R.U. of chorionic gonadotropin\* (smaller doses are ineffective) is injected daily intravenously into an infantile rabbit for five successive days, a uterine bleeding can be produced, sometimes uprooting the whole endometrium. The subepithelial vessels together with the neighboring epithelium are frequently torn, thus enabling the blood to enter into the uterine cavity and finally into the vagina. Bleeding takes place only in proliferated mucosa, never in a progesterone mucosa. It can be compared to the anovular bleeding in women. There is, however, one characteristic difference. In the rabbit we observe only shedding of the epithelium but never, as in the woman, of the deeper layers of the endometrium. What interests us here, however, is the possibility of bringing about a bleeding in a test animal which never bleeds spontaneously. Since we were not able to produce a bleeding in a castrated rabbit by means of gonadotropin, it was evident that the bleeding was induced by way of the ovary. Bleeding cannot be achieved with progesterone. On the contrary, progesterone has an inhibitory effect. It can, however, be accomplished with estrogenic hormone—and this only if a dose of 500 I.U. of estrone in aqueous solution is injected intravenously in two portions with an interval of 12 to 24 hours. After five days bleeding takes place. Does the hormone act per se, or does it stimulate some other gland to produce the bleeding factor? Greep and I<sup>15</sup> carried out experiments on hypophysectomized or adrenalectomized immature rabbits. These animals also reacted to intravenous treatment with estrone with intrauterine bleeding. Although bleeding has been observed less frequently after hypophysectomy or adrenalectomy than in normal animals there seems to be no basis for assuming that the action of estrogen is other than direct. P. E. Smith had already demonstrated that the bleeding response to estrogens and to progesterone is not greatly changed in completely hypophysectomized monkeys. In addition, Edgar Allen reported an experiment on two monkeys from which the adrenals had been removed with subsequent maintenance by cortical hormone, in which the estrin deprivation bleeding occurred perfectly well. All these experiments show that the estrogenic hormone per se can produce the bleeding and that it does not mobilize a bleeding-inducing substance in another endocrine gland.

In summarizing, we can say the following: Uterine bleeding can take place from an endometrium in a variety of functional conditions, from an atrophic, proliferated, hyperproliferated, glandular-cystic proliferated, or progestationally developed mucosa. The development of the vessels in these different functional stages varies considerably. They are the most marked, particularly as

\*The same effect can be achieved with mare's blood gonadotropin.

far as the coiled arterioles are concerned, in the premenstrual phase, while in an atrophic mucosa the vessels are developed poorly or not at all. Bleeding can occur as a result of withdrawal of estrogenic hormone, progesterone, or other steroid hormones. However, bleeding can also occur with a constant hormone level, that is, without withdrawal of the estrogenic growth stimulus.

Since bleeding can take place at such widely varying phases in the development of the endometrium, with such different degrees of vascularization, and with either decreasing or constant hormone level, the mechanism cannot be the same in every case of bleeding. In seeking a common factor, one is tempted to assume that one or more metabolites from the group of steroid hormones (particularly estradiol and progesterone) are capable of producing a bleeding by local action upon the blood vessels, regardless of the stage of development of the vessels and of the endometrium.

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## AN EFFECTIVE CLINICAL APPROACH TO ABNORMAL UTERINE BLEEDING

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WHILE I have already discussed some of my experiences in treating women with disturbances of uterine bleeding,<sup>1, 2</sup> the perpetuation of confusing concepts in this area of gynecology prompts me to review the problem and to describe a simple clinical program for the management of nearly all patients with such complaints. Even the latest textbooks and monographs which deal with uterine bleeding are not particularly helpful to the average physician seeking a solution for a specific situation because, with perhaps one exception,<sup>3</sup> they fail to organize the multitude of diagnostic entities into a logical scheme which enables him to match symptoms and diagnoses.

What we really want to discover first, when confronted by a patient whose pattern of bleeding appears abnormal (at least to the patient), is whether the bleeding complained of represents a disturbance of *menstruation*—in the strictest sense of this term—or whether it is related to a functional or to an organic lesion entirely beyond the bounds of true menstrual function. To separate uterine bleedings on this basis one must, of course, adhere to the fundamental concept that menstruation, by definition, means only one thing—cyclic bleeding from endometrial tissue which has been carried through the phase of secretion by the action of progesterone. This endometrium, in other words, has been prepared for the reception of a fertilized ovum and is often referred to as progestational endometrium. I am well aware of the academic objections to this concept, based on the presumed details of endometrial vascular physiology, but I maintain that it is exceedingly helpful to the clinician if he can discover whether his patient is menstruating or merely bleeding from the uterus.

### Clinical History

Fortunately for all concerned, it is possible very often to arrive at a satisfactory judgment about the presence or absence of true menstruation simply by obtaining a reliable history. On the other hand, few patients come with details documented, so one must dig out bit by bit the few facts which may be available and check them against a calendar for specific time relationships. This will demonstrate rather quickly the reliability of the patient's initial statement regarding the nature of her disorder, and not infrequently may indicate that in reality no problem exists. For example, it is common for a woman to complain of bleeding *twice* in a single month. Further examination of such a story may reveal merely a minor shortening of the cycle, with the result that



some parts or even all of two successive menstrual episodes occurred within the time of a single calendar month. In other instances the extra bleeding may be shown to have been related to the presumed time of ovulation and to have differed qualitatively from the usual menstrual flow. Minor problems of this sort obviously require no immediate therapy, but do warrant continued observation and careful recording of the history as it develops throughout subsequent weeks and months.

If another period of seemingly abnormal bleeding appears, the patient should be told to come for re-examination at once—that is, *while the bleeding is in progress*. Only by actual observation of the problem at its worst can the physician evaluate the situation accurately and demonstrate beyond any doubt the precise locale of the bleeding. The reluctance of some women to be examined while bleeding vaginally has been, and in some areas is still, a serious obstacle to gynecologic diagnosis. But, as in other branches of medical practice, there is no satisfactory substitute for prompt and thorough examination of the region in which the presenting complaint seems to be focused.

Another kind of problem which may be assessed quite well by a proper history is that of *menorrhagia* or *hypermenorrhea*. While some patients complain specifically of profuse and prolonged menses, a considerable number of women are reluctant to mention these phenomena or perhaps have come to accept them as necessary evils. Often the facts are brought out coincidentally in taking the history of some unrelated complaint, but only when quantitative details are elicited is it possible to evaluate the situation fully. Far too many women have been treated for anemia perpetuated by inordinate amounts of uterine bleeding, without any serious thought having been given to correction of the primary disorder. Bleeding which persists for more than seven days, which cannot be contained by a single perineal pad, or which is accompanied by the expulsion of sizable clots, must be considered abnormal. With rare exceptions it is nearly always possible to find a satisfactory organic explanation for these menstrual excesses once their existence has been well established. In other words, the problem is to find what it is in the uterus which has caused a tolerable situation (normal menstruation) to be transformed, either abruptly or gradually, into a distinctly pathological state.

Similarly, a good history is of the utmost importance in leading to a correct diagnosis of bleeding associated with an abnormal pregnancy, particularly a pregnancy outside of the uterine cavity. Often the period of amenorrhea at the onset of pregnancy is not of sufficient length to make the patient think of this possibility, or perhaps the possibility of pregnancy is deliberately avoided in the patient's initial recitation of her story. In any event, the wise physician always considers pregnancy when he is confronted by unusual bleeding from the uterus and proceeds to substantiate or discredit his suspicions by tactful but nevertheless pointed questioning.

### Classification of Uterine Bleeding

To have served its purpose, the history should enable one to narrow the diagnostic possibilities to just a few items to be chosen from a list which repre-

sents the common and clinically important causes of abnormal bleeding. Such a list need not be lengthy, but the various entities in it must be arranged so that they may easily be related to symptomatology.<sup>2</sup>

In considering first the disturbances of menstruation, as already defined, one is most often concerned with an abnormality of *quantity* or of *duration* of flow. When the flow is too profuse, or when it persists for too long a time (or both), we must seek an explanation for *hypermenorrhea*. The common answers are: (1) myomas, particularly those which distort the contour of the endometrial cavity; (2) endometrial polyps; (3) irregular shedding of the endometrium<sup>4</sup>; and (4) adenomyosis uteri interna. Certain diseases of the blood attended by defects in bleeding and clotting mechanisms may be associated with hypermenorrhea, but these are rare and seldom are encountered initially by the gynecologist.

The converse of hypermenorrhea is, of course, *hypomenorrhea*, characterized by menstrual bleeding which is scanty and of short duration. The quantitative limits of this situation are less well defined and one can say little about its causation beyond the vague statement that it may have its basis in endocrine dysfunction. Fortunately, it is not a problem which presents a serious clinical threat to the patient and should require only a simple explanation of our present inability to understand or to change it. Ill-conceived efforts to treat hypomenorrhea with hormonal preparations must be discouraged.

The other fundamental menstrual disturbance is that of *timing*, or interval between bleedings. If the menses appear too frequently, one may say that the patient is suffering from *polymenorrhea*. While the length of the shortest possible complete menstrual cycle is not known, rarely does anyone bleed repeatedly from secretory endometrium at intervals of less than twenty days. Women who claim to have a cycle of three weeks ordinarily exhibit cycles ranging in length from 20 to 25 days, while those who believe they have a four-week pattern actually have cycles varying in length from 25 to 33 days. Simple shortening of the cycle, whether habitual or occasional, is not a problem which demands treatment.

A rather frequent complaint is that of premature interruption of the cycle, a situation in which a woman accustomed to a four-week cycle suddenly experiences a menstruation-like period of bleeding which begins far too early. We can only speculate about the basic factors responsible for setting off prematurely the presumed humoral-neurogenic chain reaction which culminates in bleeding,<sup>5, 6</sup> although not infrequently there seems to be an emotional basis if one takes the time to look for it. Since these patients cannot anticipate their out-of-phase bleedings, it seems unlikely that we shall ever be able to categorize with certainty the prebleeding histologic pattern in the endometrium, and indeed it may not, of course, always be the same. In any event, these unforeseen and unwanted bleedings tend to be self-limited and nonrecurrent, and therefore require nothing more than observation.

The opposite of polymenorrhea is *oligomenorrhea*, characterized by exceptionally long intervals between menses. It has been assumed that most women with this complaint are experiencing prolongation of the proliferative phase of

the cycle and delayed ovulation. However, it is not particularly uncommon to find that the secretory phase of the cycle has been prolonged by persistence of a corpus luteum for a week or two beyond its usual expiration date. The subsequent flow is likely to be profuse and prolonged, simulating the bleeding which occurs with irregular shedding of the endometrium. One may, on occasion, be able to palpate the enlarged ovary containing the corpus luteum, and, if curettage is done before extensive loss of endometrium has occurred, the marked decidua-like appearance resulting from prolonged progesterone stimulation may be seen.

Besides the disturbances which may be related in one way or another to menstruation (as defined previously), it is possible to construct at least two categories of *nonmenstrual bleedings*. The first comprises a group of bleeding problems which are rather clearly estrogenic in origin, and includes such entities as endometrial hyperplasia, bleeding associated with ovulation (estrogen deprivation?), and bleeding which follows the administration of estrogens to postmenopausal women. To this group must be added the prolonged and irregular bleeding which occurs from proliferative endometrium without the characteristic changes of classical hyperplasia. Perhaps an endometrium of this sort is hypoestrogenic—at least some of them appear to be so when viewed histologically—although this is a concept which cannot readily be substantiated in the absence of a suitable assay for blood estrogen. In any event, women with such endometria do not ovulate with any regularity, and their bleeding disturbance in a sense is a variety of *anovulatory bleeding*. This term, however, by common usage denotes regularly recurring bleeding, of modest duration, from proliferative endometrium. To all outward appearances it is identical with true menstrual bleeding but has often been called pseudomenstruation because of the lack of progestational changes in the endometrium. In this sense, anovulatory bleeding cannot be considered a disturbance of uterine bleeding since by clinical criteria alone it does not appear to be abnormal.

The ultimate in anovulatory bleeding is represented by bleeding from an atrophic or senile endometrium in a postmenopausal woman who has neither ovulated nor bled vaginally for a number of years. This is a sufficiently common situation to warrant giving it separate consideration, but it is unwise to invoke this diagnosis without conclusive histologic proof that no other lesion exists.

The second group of nonmenstrual causes of bleeding is a miscellaneous array of lesions not primarily concerned with the physiologic functioning of the endometrium. These are specific organic lesions not necessarily concerned merely with some disruption of the bleeding pattern, but often masquerading as a bleeding problem until such time as the true situation is recognized. For example, an abnormal early pregnancy (particularly an ectopic gestation) is likely to exhibit unusual bleeding as one of its first signs, or a pregnancy long since aborted may continue to be the source of bleeding because of subinvolution at the placental site. Carcinoma at various levels in the generative tract—vagina, cervix, corpus, even in the tube—must always be given proper

consideration as the source of bleeding, and in rare instances endometrial infection (usually tuberculosis) may be the agent. It is helpful to include with these causes of metrorrhagia or of postmenopausal bleeding the pair of polypoid lesions already considered in conjunction with hypermenorrhea, namely, submucous myoma and endometrial polyp. Such structures conceivably may bleed at any time during the menstrual cycle and are not to be considered exclusively as instigators of menorrhagia. To complete the picture, one should include the lowly cervical polyp which on occasion may produce bleeding of an alarming degree and which regularly is indicted as a cause of intermenstrual spotting; and occasionally vaginal trauma is the obvious source of trouble.

To summarize, all of the items just mentioned may be fitted together into some such simple scheme as the one which follows. A classification of this kind serves admirably as a catalyst to convert signs and symptoms into diagnoses, and once a diagnosis has been made the treatment usually is rather obvious. The outline seems to contain all the common causes of disturbed uterine bleeding, although one may expand it almost *ad infinitum* if he wishes.

#### ABNORMAL UTERINE BLEEDING

##### A. Disturbances of menstruation

###### I. Concerned with quantity and/or duration of flow

###### 1. Too much and too long (hypermenorrhea)

- a. Myoma
- b. Endometrial polyp
- c. Irregular (delayed) shedding
- d. Adenomyosis uteri

###### 2. Too little and too short (hypomenorrhea)

(No gross organic lesions)

###### II. Concerned with timing of flow

###### 1. Too frequent (polymenorrhea)

- a. Basically short cycle
- b. Premature interruption of cycle  
(Various causes?)

###### 2. Too infrequent (oligomenorrhea)

- a. Delayed ovulation
- b. Persistent corpus luteum

##### B. Nonmenstrual disturbances

###### I. With estrogenic basis

- 1. Endometrial hyperplasia
- 2. Ovulation bleeding
- 3. Bleeding following administration of estrogens
- 4. Bleeding from hypoestrogenic, anovulatory endometrium
- 5. Atrophic (senile) endometrium

###### II. Due to miscellaneous lesions

- 1. Disturbed pregnancy (abortion, ectopic, hydatid mole)
- 2. Carcinoma (vagina, cervix, corpus, tube)
- 3. Polypoid lesions
  - a. Cervical and/or endometrial polyp
  - b. Pedunculated submucous myoma
- 4. Endometrial infection
- 5. Vaginal trauma



### Decisions as to Treatment

Careful physical examination, in addition to the detailed type of history already described, will occasionally reveal the correct diagnosis at once, and one may then take whatever steps seem desirable to eliminate the lesion in question. This applies, however, only to some of the myomas, some of the polyps, some of the cancers, and some of the disturbed pregnancies.

A second group of patients who may be disposed of fairly promptly are those with essentially normal physical findings and histories indicating that (1) the situation is not serious either as a potential cause of anemia or as a conceivable indicator of cancer, and (2) that nothing of real importance could be done about it even if the precise diagnosis were known. In this category I would place most of the disturbances of menstrual timing, ovulation bleeding, and hypomenorrhea. These are problems for watchful expectancy, which means that the patient is instructed to keep an accurate record of her performance and report the details at definite intervals. Occasionally intermenstrual bleeding which is presumed to be related to ovulation may be so voluminous or of such long duration as to require curettage to eliminate all possibility of an associated organic lesion. Rarely the bleeding which follows a persistent corpus luteum is so profuse that curettage seems necessary for hemostatic purposes; in such a case, of course, the diagnosis becomes clear only in retrospect.

We are left, then, with a large residue of patients who have no striking physical abnormalities but whose stories indicate that something should be done reasonably soon to either (1) control excessive bleeding or (2) rule out the possibility that the bleeding in question may be associated with a malignant process somewhere in the generative tract. These are the women with hypermenorrhea, those with totally irregular bleedings of variable length and quantity (estrogenic basis), and those who are bleeding after the menopause. Since curettage of the uterus, properly done,<sup>7</sup> is both hemostatic and diagnostic, it is our most effective weapon under these circumstances. Patients with cyclic hypermenorrhea should be curetted on the fifth to the seventh day after the onset of bleeding, since only in this way can irregular shedding of the endometrium be discovered.<sup>4</sup> In the totally irregular bleeders, curettage may be done at any time, but preferably at the onset of an episode in order that the endometrial layer may be seen in its full thickness. On the other hand it is often not justifiable, in the interest of a better histologic specimen, to postpone curettage appreciably longer in a patient who has been bleeding continuously for many weeks. Women with postmenopausal bleeding should be subjected to curettage promptly.

Curettage provides not only a diagnosis and often a cure, but at the same time affords an opportunity to carry out a thorough pelvic examination under anesthesia. This can be of the utmost importance in evaluating vague masses and indurations with a view to future surgical management. At the same time a cervix which may have been difficult to evaluate by office examination alone can be observed at close range under good light, and biopsy specimens may

be removed without fear of bothersome hemorrhage. In selected patients, culdoscopy may add still further to the complete assessment of the reproductive tract.

Steroid hormone therapy is not used in women with disturbances of bleeding until a definitive diagnosis has been made. Actually there is no situation other than that of endometrial hyperplasia in which endocrine therapy might be expected to be beneficial. The indiscriminate prescribing of either estrogens or androgens must be condemned, and the mere fact that certain patients stop bleeding after the use of these substances is not proof that they were of the slightest benefit. In patients with hyperplasia, however, the carefully planned cyclic administration of progesterone has been almost universally accepted as a reliable procedure to produce self-limited bleeding from progestational endometrium.<sup>8</sup>

### Clinical Material

In the period of six years from the beginning of 1948 through 1953 my limited personal practice, conducted in conjunction with a geographic full-time teaching position, has yielded 109 patients who were subjected to curettage of the uterus. Five were curetted twice, making a total of 114 specimens. On ten occasions the curettage was done simply to complete obvious abortions or as an adjunctive procedure when an obvious lesion of the cervix was biopsied or treated under anesthesia, and these specimens will not be considered here. In the remaining 104 instances curettage was done because the etiology of the uterine bleeding was obscure and it was hoped that satisfactory explanations might be found. With rare exceptions, curettage was done at specific times in the menstrual cycles, or in relation to episodes of bleeding, as has already been described, and not at the convenience of patient, operating room staff, or operator. The diagnoses resulting from the examination of these 104 endometrial specimens, as well as those previously reported in a smaller series,<sup>2</sup> are shown in Table I.

TABLE I. CAUSES OF ABNORMAL UTERINE BLEEDING IN WOMEN SUBJECTED TO DIAGNOSTIC CURETTAGE OF THE UTERUS

CAUSE	PREVIOUS SERIES*	1948-1953
Hyperplasia of the endometrium	10	24
Endometrial polyp	8	22
Irregular (delayed) shedding	4	18
Submucous myoma (normal endometrium)	5	15
Atrophic (senile) endometrium	2	7
No obvious cause (normal endometrium)	5	6
Hypoestrogenism with anovulation	0	4
Subinvolution of placental site	0	2
Proliferation due to exogenous estrogen	0	2
Adenocarcinoma of the endometrium	0	2
Decidual reaction with persistent corpus luteum	1	2
Total	35	104

\*See reference 2.

It may be seen that hyperplasia, polyps, irregular shedding, and submucous myomas are the major problems. Myomas were present in more than

the 15 uteri listed but were not considered as the primary diagnosis when any other logical explanation for bleeding was found. In some of these instances, of course, the myoma may have contributed to the disturbed bleeding fully as much as the other lesion.

The occurrence of endometrial polyps in somewhat over 20 per cent of the specimens corroborates Scott's<sup>9</sup> recent statements about the importance of this lesion as a cause of bleeding, particularly premenstrual and postmenstrual spotting as well as menorrhagia. Polyps must be sought within the uterine cavity by using a suitable clamp at the time of curettage; they should be removed from the general mass of curettage fragments and imbedded separately to insure their microscopic identification.<sup>7, 9</sup>

Of the five patients who were curetted twice, two had recurrences of irregular shedding, two developed additional endometrial polyps, and one exhibited further prolonged bleeding from a uterus studded with small myomas. This myomatous uterus continued to bleed abnormally and was removed four months after the second curettage.

Only 6 of the 99 cases failed to reveal either a gross or microscopic lesion to explain the bleedings. In all of these instances it is likely that the historical data had been exaggerated or falsified, for various reasons, and undoubtedly the curettements could have been avoided had further time for observation been demanded. In any event, the production of specific diagnoses in 94 per cent of the trials is heartening both to patients and to physician, and I believe, is ample demonstration of the value of the program already outlined. When a diagnosis has been made, treatment usually is a simple matter if perchance the diagnostic procedure has not been at the same time therapeutic. In a subsequent paper the postcurettage events in the gynecologic histories of this group of women will be presented in detail.

### Summary

A plan is presented for the clinical management of women who complain of abnormal uterine bleeding. This is based on the use of a simplified classification of the causes of bleeding, a scheme which attempts to separate menstrual aberrations from nonmenstrual bleedings by means of accurate historical and histological data. Curettage is advised both as a diagnostic and therapeutic device when the bleeding in itself is of clinical importance from the standpoint of quantity or duration, or when there is great likelihood that the bleeding, however insignificant, may point the way to a malignant process.

In a period of six years, 99 women were assessed in this manner and curetted on 104 occasions at times selected with a view to disclosing specific endometrial lesions. By correlation of history and gross pelvic findings with histologic details, it was possible to reach definitive diagnoses in 98 instances, and thus to proceed intelligently when further therapy was indicated. The lesions found most commonly were endometrial hyperplasia, endometrial polyps, irregular shedding of the endometrium, and submucous myomas.

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## **FORTY YEARS' PROGRESS IN THE TREATMENT OF FEMALE STERILITY**

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**P**ROGRESS in medical and surgical treatment during the last four decades has been manifold and epochal. Keeping pace with this progress, advances in treating sterility have been in some respects equally marked. The fundamental changes which treatment of sterility has undergone in this period of time were due chiefly to newer concepts of pathogenesis and to accelerated progress in physiology and endocrinology, especially the latter. To a certain degree, these were stimulated by the facility of nonoperative methods of determining the continuity or blockade of the upper portion of the female genital tract, methods which have been made available between 1914 and 1920. Since then, more accurate knowledge of the physiology of the endocrine glands and their interrelated influence, especially on the ovary, has gradually emerged. Perhaps the most important of the gains in knowledge has been the light thrown on the process of ovulation and its aberrations.

Many operative and nonoperative interventions carried out in the early decades of the present century were based on an inadequate awareness of the function of the female genital organs and their interrelations with the pituitary, thyroid, and adrenals. As the reciprocal relations between the endocrine system and the genital organs became better understood, many surgical procedures formerly designed for the relief of dysmenorrhea, leukorrhea, and menometrorrhagia, for example, besides sterility, have either been abandoned altogether or greatly limited in their therapeutic indications.

Among the procedures which were much abused may be particularly mentioned cervical dilatation and curettage and semimutilating cervical operations undertaken on an entirely empiric basis for the relief of dysmenorrhea and sterility. These procedures appear illogical now in light of the fact that often the true cause of reproductive failure actually lay deeper, in the genital tract, i.e., in the tubes or the ovaries. Except when an organic stricture is present within the cervical canal which may cause dysmenorrhea and sterility, few gynecologists nowadays perform discissions, plastic widening of the external os of the cervix, or even simple dilatation and curettage for the relief of these functional disturbances.

Operative treatment was often wrongly based upon faulty evaluation of symptomless anatomical variations of the position and angulation of the uterus; upon flexions and versions which were accordingly subjected to many surgical procedures. To what extent the different types of suspensions and fixations actually brought relief to the complaining woman was determined only after

many thousands of these operations were performed, the end results of which were judged by a regular follow-up examination first inaugurated and adopted some forty years ago by many hospitals in this country. The follow-up of innumerable patients after these operations in addition to newer concepts of gynecologic pathology and function have enabled us to arrive at a more rational plan of therapy.

Older gynecologists of the present generation will recall discussions of the so-called pathologic entity known as metropathia hemorrhagica. The question of visceroptosis occupied the attention of the specialty as well as of the general profession during that period. Certain gynecological conditions were held to be part and parcel of visceroptosis, which was prominently featured in the transactions of gynecological societies.

The reciprocal relations of diseases of other organs and systems of organs to genital disease began to be appreciated in the first decade of the present century. This marked a departure in the interpretation of symptoms, which had a profound effect on gynecological surgery. The neurogenic and psychogenic relations of dysmenorrhea are a familiar example.

Gynecological terms in common use at the turn of the century and for two or three decades thereafter, such as essential or idiopathic uterine bleeding, recall some obscure concepts of functional states accepted by textbook authors of that time. They were supposed to designate manifestations of gynecic disease for which no ascertainable local genital pathology or constitutional abnormality was demonstrable. The elucidation of adenomyosis and of endometriosis has resulted in a clarified view of this hitherto ill-understood condition. From this nebulous concept of the principles of treatment of sterility there has evolved a systematic discipline embracing operative and nonoperative measures for the correction of pathological and functional faults inherent in the genital organs, in interrelated neighboring and remote organs, as well as disturbances of the psychic and somatic constitution. It goes without saying that treatment of the female partner of a sterile mating is necessarily integrated with study of the husband's genital and general condition and is undertaken only after a thorough investigation of all the sterility factors in both has been made and the deficiencies or barriers to fertility have been carefully evaluated.

Perhaps the progress achieved in the last forty years in the treatment of sterility can best be appreciated by a résumé of the various procedures commonly accepted and practiced in an effort to remove what are nowadays considered highly plausible and well-established barriers to fertility in the female. In this scheme the genital tract is considered from its external to internal parts and reference will be made to constitutional and other faults which have to be included in the treatment of the complex factors involved in sterility.

#### **Causes of Sterility in the Lower Genital Tract**

Measures against vulvitis and vaginitis have improved. There is a more rational therapy based upon a better understanding of the secondary changes due to deficient hormonal supply. Thus, in children, obdurate vaginitis is

quickly cleared up by use of estrogens, preventing synechiae and other changes which act as fertility deterrents later on. The incidental release of these unfortunate children from the vigorous treatment to which they were formerly subjected is an incalculable boon. Though less difficult to treat in adults, vaginitis can act as a deterrent which when eliminated by adjunctive hormonal therapy leads to more favorable reception of spermatozoa and fertility.

Whether or not *Trichomonas vaginalis* is responsible for hostile effects upon spermatozoa, its importance as instigator of vaginitis has been recognized in the past two decades and measures to rid the organism of this infestation have vastly improved.

Acute and chronic endocervicitis and cervicitis, lesions which have special etiological importance in female sterility, were formerly almost intractable to treatment. These conditions can now be quickly alleviated by oral and topical administration of antibiotics with or without sulfonamides. What difference this makes to the patient those of us who practiced gynecology more than thirty years ago are in the best position to estimate. Suffice it to say that when one accomplished some degree of relief from cervical and vaginal discharge after 3 to 6 months of daily applications of antiseptics and many suction treatments, the sense of therapeutic despair was to some degree lessened.

The methods of partial cervical amputation, of conization and light scarification with the nasal cautery which were developed in the meantime for the relief of cervical discharge with a varying measure of success are now likely to be largely supplanted by antibiotics and chemotherapy. It has been recognized that cervical synechiae and stenosis often follow in the wake of these procedures with the electric cautery when not carefully carried out, producing artificial barriers to fertility which necessitate correction later.

A favorable influence on the character of the cervical mucus is effected by the administration of estrogens which renders the thick viscid secretion thinner and less tenacious and thus promotes the ascent of spermatozoa. Also, in hypoplastic conditions of the uterus in which the cervix participates, a sparse mucus secretion from a relatively dry cervical canal may be stimulated to produce more nearly normal mucus secretion which exerts a favorable influence on sperm migration.

#### **Causes of Sterility in the Uterus**

As far as the uterus is concerned in relation to sterility, perhaps a better appreciation has been gained of the so-called hypoplastic uterus, or more appropriately termed underdeveloped uterus, in connection with the endocrine system. Although not definitively settled, attempts at determining degrees of underdevelopment by estimating the ratio of the length of the cervix to that of the uterine cavity have given some idea of the deficient development of the uterus in sterile women by comparison with similar measurements of parous uteri.

A better notion of the size of the uterine cavity is obtained by hystero-graphy, provided the same amount of contrast medium is employed for the intrauterine injection as in the case of uteri of parous women. By this same

method, uterine polyps, hypertrophic endometria, submucous myomas, adenomyosis, and uterine synechiae, the result of too vigorous curettage, especially after abortion, can be diagnosed. Malformed uterine cavities resembling none of these lesions sometimes suggest the presence of endometrial tuberculosis. Anomalies such as bicornate, arcuate, and double uterus without double cervix are possible to diagnose only by means of hystero-graphy. Each peculiar roentgenologic finding indicates the appropriate therapy which need not be entered into here.

Carcinoma is so rarely encountered in the younger group of sterile women as to require little discussion. In the older group of nulliparas it must be thought of and excluded before operative interventions are undertaken for associated lesions, principally fibroids. The latter tumors have been amenable to removal with a remarkable progress in lessened morbidity and practically no mortality. Whereas multiple myomectomy was fraught with a relatively high postoperative morbidity forty years ago when few gynecologists and general surgeons ventured the more conservative operation for fibroids, the mortality rates during the last two decades have dropped below those following the various types of hysterectomy or have at least equaled its low incidence. The salvage of the uterus and the psychological emotional satisfaction to infertile women with fibroids need no further emphasis. By and large from 30 to 50 per cent of women who have been operated upon by multiple myomectomy have become mothers.

Advances in general medicine, such as improved measures to prevent and combat shock, the replacement of blood loss by transfusion, and safer and less toxic general anesthesia, besides the availability of antibiotics, are largely responsible for the successful performance of myomectomy. Special technical advances in the operation itself, however, account for the good results to an appreciable extent. A notable contribution to preventive hemostasis by specially constructed broad ligament clamps and the trans-broad ligament pericervical tourniquet has enabled us to remove safely many dozen myomas from the uterus, sometimes aggregating 80 or more, with the least possible blood loss and no shock. The use of the endotherm knife has also proved advantageous in reducing blood loss usually attending myomectomy.

Ventrosuspension, which was excessively done in the early decades of this century and has since been more or less discarded, has usefulness in certain cases. The indication for ventrosuspension has been greatly aided by the preliminary use of uterotubal insufflation which determines whether the Fallopian tubes are angulated or obstructed as a result of the distorted position of the uterus. A preliminary trial of positional correction by suitable pessaries of the retroverted uterus in case tubal obstruction is found has been an advance in the direction of rational therapy. If the tubes remain patent while the uterus stays in normal position supported by the pessary, there would be no point in doing a laparotomy except for exploratory purposes to inspect the ovaries, etc., which is not often justified.

Thus more rational indications have been developed for older surgical procedures which were previously adopted on a more or less haphazard basis.



### Causes of Sterility in the Fallopian Tubes

When we consider the tubes, perhaps the greatest advance was made in the matter of the diagnosis of their patency or nonpatency. If nonpatent, the indication for needless and useless operations on the cervix and uterus *per se* is immediately negated unless a laparotomy is undertaken at the same time in an attempt to relieve the obstruction. The very methods of diagnosing tubal patency have been found to have therapeutic value. Uterotubal insufflation by itself has been successful in relieving sterility due to various degrees of tubal obstruction in over 20 per cent of the cases, while hysterosalpingography has been claimed to have an equal or lesser incidence of success. These two non-operative methods have marked a decided advance in therapy though their chief value has been their diagnostic aid. When they are combined with other measures, such as pelvic diathermy, nonspecific protein therapy, and small dosage of estrogens which promote tubal as well as pelvic hyperemia, the adhesions surrounding the tubes are loosened while in some cases there is even tubal epithelial regeneration and recanalization of the obstructed tubal lumen.

On the surgical side, thanks to general surgical advances and an increased interest in restoring tubal patency, some progress has been made. Though not substantial, the successful results are better than were achieved formerly, approaching in some reports 20 per cent or over. Considering that a 5 to 10 per cent result was previously regarded as the best obtainable after plastic reconstructive operations on the Fallopian tubes, the improvement is appreciable. The auxiliary use of uterotubal insufflation during and after the operation and the use also of hysterosalpingography with water-soluble iodine contrast media have helped in some measure to achieve the better results. Recent attempts to improve previous results include the use of plastic prosthesis of polyvinyl ethylene tubing. When we recall that tubal obstruction was regarded in the early part of the century as quite irremediable, the results obtained since then are gratifying. There is, however, more work still to be done in this field. But perhaps modern methods of prevention of, and of effectively treating, acute salpingitis offer the best hope for the future.

There remains one type of tubal infection, namely, tuberculosis, which, formerly regarded as hopeless from the viewpoint of therapy, has more recently become amenable to treatment. The incidence of tubal tuberculosis in some geographical areas is 5 per cent in sterile women. In one area, Sweden, it is said to be as high as 19 per cent. Endometrial biopsy has been of great help in diagnosing the presence of genital tuberculosis. Formerly only suspected but not demonstrable except by histologic examination of the excised tubes, this condition is demonstrable to a large degree by endometrial biopsy. The finding of tubercles in the histologic section and the demonstration of the tubercle bacillus from cultures of the endometrial secretion leave no doubt of the diagnosis. There are certain distortions of the uterine cavity and the lumen of the tubes as seen on the hysterosalpingograms that are strongly suggestive of tuberculous endometritis and/or salpingitis. By use of dihydrostreptomycin combined with para-amino salicylic acid, some cures have been recorded, while

pregnancy has been observed in a few rare cases. The finding of tubal obstruction by the safe method of kymographic uterotubal insufflation with carbon dioxide should invariably lead to taking an endometrial biopsy. Although endometrial tuberculosis is comparatively rare in our country, it is well to be able to exclude this specific infection as the basis of any given case of sterility in which tubal obstruction is demonstrated.

A marked change has taken place in the last two decades with respect to the treatment of endometriosis. At first, the general trend was to do radical extirpation of the uterine adnexa and even the uterus. Many young women were thus needlessly sterilized. By the use of male hormones some of these patients can be benefited to the extent that they become pregnant, while surgery, if resorted to, is more conservative. This is decided progress. To be sure, there are some cases of massive endometriosis that are not amenable to androgen therapy, resisting even the heaviest doses. For such cases x-ray therapy is better than hysterectomy. Because of the patient's youth, she may regain her menses while the crippling effects of the endometriosis may disappear. An advantage of x-ray therapy over male hormone therapy is the avoidance of masculinization which frequently follows large doses of testosterone treatment.

#### **Causes of Sterility in the Ovaries**

As far as the ovaries are concerned, surgical concepts of treatment have undergone marked changes for the better. One need only recall the impunity with which ovaries were removed prior to forty years ago due to disregard or ignorance of their important role in the body economy and partly because it was feared that they would only serve as a focus for carcinomatous, or at best, cystic, degeneration. In older women requiring hysterectomy for fibroids, the ovaries were routinely removed, and castration was resorted to even in adolescents, in order to control uterine bleeding. Here hormonal therapy has had signal success with or without the aid of blood transfusion and other hematinics besides thyroid therapy. Functional menometrorrhagia of young adults can be relieved in a similar manner and the menses restored to regularity, so that eventually conception becomes feasible. Surgical treatment in such conditions, as practiced since 1918 and 1919, consists in removing the microcystic portion of the ovaries and leaving enough cortex for further follicle maturation. The same treatment has been used for the relief of amenorrhea and sterility with a tolerable measure of success. A number of reports definitely point to the beneficial effects of this conservative form of partial ovarian resection.

There are, however, two nonsurgical measures for the relief of sterility associated with amenorrhea that compete closely with subtotal ovarian resection and which have been used in the past three decades. The first is fractional-dose x-ray irradiation to the ovaries and the pituitary; the other is gonadotropin and estrogen therapy. Over 80 per cent of the patients treated by low dosage x-ray irradiation to the ovaries and the pituitary have become regular in their menses and 50 per cent have become mothers. Considering that from 6 to 10 per cent of the untreated patients become spontaneously pregnant, the in-

crement of success is quite appreciable. The fruit fly experiments, however, have been interposed as an objection to the x-ray irradiation therapy. The geneticists insist that there is danger of inducing lethal and mutational effects in the children born of mothers who were exposed to the x-rays. This is not the place to enter into a discussion pro and con of this hypothetical objection. So far, from observation of several thousand children born after this treatment there is no evidence to support the fears of the geneticists. There are now observations on some 17 grandchildren stemming from grandmothers who were irradiated in order to regulate their menses and to improve their possibilities for conception. The grandchildren were all normal by the criteria of comparison with other children born from mothers or grandmothers who were not exposed to such treatment. The doleful warning about a fourth, fifth, or twelfth generation appears to be posed on tenuous and debatable grounds. The children and grandchildren comprising this category so far are testimony against the assumption that human beings are like fruit flies. The physical and biological conditions of the two species are so far apart that the far-reaching conclusions of the geneticists are, *a priori*, at least as invalid as they may be valid.

As to gonadotropin therapy, the best results approximate 50 per cent as far as restoration of regular menstrual cycles is concerned, while the pregnancies that follow do not approach by a large margin the results obtained after x-ray irradiation. The reports speak of pregnancies but it is difficult to find statistics that are definite. The largest single series of patients treated with gonadotropins from pregnant mare serum and chorionic gonadotropins has been reported from Denmark and Sweden.

Surgical treatment of the ovaries in the form of subtotal resection appears not to incur such theoretical genetic risk. Gonadotropin treatment is to a certain extent subject to the same theoretical claim as has been made against fractional irradiation to the ovaries. Treatment with estrogens has not been nearly as effective in sterility associated with amenorrhea as has the use of gonadotropins. Until more adequately potent gonadotropins become available, x-ray irradiation which has so far proved to be the most successful measure for the relief of sterility associated with amenorrhea will not be denied to this particular group of nulliparous women keenly desirous of children. The decision to submit to this treatment should, however, be left to the subfertile couple to whom a clear statement is made concerning the genetic question.

### Other Causes of Sterility

The results of treatment of barriers to conception inherent in the genital organs of the female mark considerable progress compared to the results of treatment for sterility obtained forty years ago. They give reason for satisfaction but by no means justify complacency. There are, as stated above, many lacunae to fill and much more labor to be done. Not so satisfactory is the progress made in treating the constitutional barriers which are more elusive than the local genital deterrents to conception.

Conditions which inhibit oogenesis apart from genital disease are not so well understood. In general it is known that disturbances of endocrine function of other glands, chiefly the pituitary, thyroid, adrenals, and pancreas, influence unfavorably the fertilization of the ova and interfere with the ovulation process. The signs of such disturbances are unfortunately not always clear-cut. They may be subclinical and not readily observed. Treatment with thyroid has been heralded by many as efficacious in functional ovarian disturbances while some reliable observers have failed to see any definite benefit from thyroid treatment.

The harmful effects on fertility of acute or chronic infectious diseases have been claimed for some time. Malnutrition and obesity appear to exert a bad influence on ovulation; and avitaminosis has been claimed to have a similar depressing effect. Some even claim that an excessive vitamin intake produces the same harmful results. Chronic lead poisoning, alcoholism, and morphine addiction have been held responsible for ovular failure. That environmental changes, especially climatic, may produce temporary amenorrhea and sterility has become increasingly appreciated. Lack of outdoor exercise has also been recognized as a possible cause of gonadal failure. On the other hand, there has been the surmise that too much outdoor sports, too violent athletics indulged in by college girls and women may lead toward the same end. Excessive smoking and too much resort to reducing diets undoubtedly play a role in lowering fertility. Inadequate mineral intake may predispose to ovarian malfunction. Specific causes for ovarian failure are exposure to x-rays or radium in industries which require such exposure on the part of women workers. Masculinizing tumors of the ovary definitely cause amenorrhea and sterility. Their removal may, however, restore both menstruation and fertility.

### **Social and Economic Aspects**

The complexities of everyday life in a society which is subjected to strains and tensions imposed by two world wars and their impact on all phases of living cannot fail to affect the function of reproduction. The experiences of the last war point up in a most poignant way the depressing influence on ovulation of starvation alone or in combination with psychogenic and neurogenic disturbances. Without relation to the aftermath of the war, changed conditions of domesticity may affect the ovulation process to the detriment of fertility. To what extent competition of women with men in industry and executive positions is responsible for lowered fertility in these women can only be conjectured. The definitely conspicuous infertility observed in this group of women suggests that the strain of such new tasks as have been undertaken by women during the last forty years tells upon the body economy and in this instance markedly upon the process of ovulation which appears to be extremely sensitive to psychoemotional states. Appreciation of these factors enables us to regulate the physical and mental hygiene, restoring the health of those undernourished individuals by vitamins, intake of minerals, adequate calorie diet, which may increase their threshold of fertility.



Besides these conditions, social, economic, and domestic, over which gynecologists cannot be expected to exercise control, their task as physicians necessitates earnest consideration in the treatment of sterile women. Of importance in this connection are hematologic conditions such as incompatibility of certain blood groups, the Rh factor, etc., which may account for the predisposition to abortion otherwise unexplained. More intensive study of this lead is desirable. If 80 per cent of the causes of female sterility can be determined, there is much work to be done to discover the remaining deficit. As the discovery of the cause is often followed by a corrective remedy, relief from sterility in the next forty years or less should be raised from the present high estimate of 50 per cent to 75 per cent or higher, at least in some subgroups.

### Results of Therapy

Concerning the results obtained in the cure of sterility by the more comprehensive investigation possible nowadays as compared to forty years ago, it should be recalled that from 25 to 30 per cent success was claimed after operations on the cervix alone. There was, however, no attempt at establishing criteria by which to judge the results. Whether or not many of the successful results could have been obtained without the surgical intervention is only conjectural but the chances are that they were to a large extent coincidental. Nulliparous women who were thus operated upon and became pregnant were only too happy to credit the surgical operation with the successful issue. Without going further into the emotional phase of this subject it needs to be emphasized that painstaking regard must be given the matter of judging results by strict criteria such as were laid down for one of the nonoperative methods of treatment, namely, kymographic uterotubal insufflation.

There is need even today, however, of making scrupulous appraisal of results in light of the progress during the last forty years in the diagnosis of the different causes of sterility and the extent to which these causes have actually been eliminated. Even when this is achieved there is no guarantee that conception will necessarily follow in every treated case of sterility. The patient must understand this fully before any operative or nonoperative treatment is proposed and undertaken for the cure of sterility. The married couple should be told clearly that an attempt to remove the recognized barrier or barriers to fertility will be made but that as far as pregnancy resulting therefrom is concerned there is no assurance. A statement may only be made to the effect that the restoration to anatomical and functional normalcy promotes the woman's chances of conception provided always that the husband is either already known to be normal or that he is also undergoing treatment to correct faults which may be contributing to the infertility.

In the last analysis, conception depends on the combined constitutional and genital fitness and physical and emotional compatibility of the married partners. To a certain extent experience has indicated that high biological fitness on the part of one mate may compensate for the relative deficiency on the part of the other mate. This is something, however, which needs further research to clarify. To enter into an explanation at this time would only be guesswork.

I should like to pay my personal tribute to Dr. George W. Kosmak in whose honor this article has been written and dedicated. The most active years of the Emeritus Editor of this JOURNAL have been contemporaneous with the period covered in the present communication.

I deem it a rare privilege to be included in the group of friends, admirers, and colleagues of Dr. Kosmak and I am grateful to him for his outstanding services beyond his strictly professional duties as editor, teacher, scholar, medical and social educator, counselor, and guide.

## VULVAR FLUORESCENCE

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THE object of this dissertation is to review the facts concerning vulvar fluorescence to near ultraviolet light, to add some personal observations made during the last three years, and to speculate regarding the nature and significance of this very interesting phenomenon. It is my belief that such a review is timely because many gynecologists have regarded the reports on the phenomenon with suspicion, chiefly, I imagine, because of lack of experience with it, some inconsistencies in the findings reported by various observers, and/or its unexplained nature. Since I have become convinced that vulvar fluorescence in response to near ultraviolet light is a bona fide phenomenon which has both clinical and investigative possibilities I wish to express myself to that effect.

The first report dealing with this phenomenon was published in 1948 by Dr. Sydney Margolese.<sup>1</sup> A subsequent article was published by Margolese and McDonald<sup>2</sup> in 1950. In making their observations these men utilized a General Electric CH<sub>4</sub> mercury arc spot lamp with a No. 5874 Corning filter. This light source emits radiations in the neighborhood of 3,650 angstrom units and while the filter employed does not cut out all visible radiations they are reduced to a reasonable minimum. Anyone employing this setup must become accustomed to the light blue visible radiations emitted so that differentiation can be made from the purple fluorescence characteristically excited by the specific radiations mentioned. Care must be taken to remove all extraneous materials such as lubricant, powder, secretions, etc., from the surface of the skin, since such materials may themselves give rise to fluorescent phenomena. The examinations were made in a dark room with the patient in the lithotomy position and the lamp held approximately six inches from the vulva. An attempt was made to record not only the intensity of the purple fluorescence but also its extent, and both were arranged on a scale of 5. Subsequently the results of examinations made while employing essentially an identical technique were reported by Benson, Strait, and Chappell,<sup>3, 4</sup> and by Greenblatt.<sup>5</sup> During the last three years, in conjunction with Drs. Sydney Margolese, Darphus Omeron, and Bawa Prehlad Singh, I have examined a large number of women exhibiting a variety of gynecological states. The technique employed was that of Margolese described above.

All observers are agreed that: (1) There is no fluorescence of the vulva in childhood. (2) A purple color of varying extent and intensity can be seen

on the vulva between puberty and the menopause, and sometimes in old age. (3) A darker but also variably intense purple is visible during pregnancy which fades rapidly at the termination of pregnancy. (4) After the onset of menstrual life there appears on the vulva a greenish background fluorescence observable at the edges of the purple, and when the purple is absent, as in castrates and postmenopausal women. Benson describes a brownish color replacing the green in elderly women. Since the green referred to previously has a yellowish brown tint and is of sickly hue, we believe that the brown which he described is actually a variation of the green described by others.

Without question red fluorescence of the vulva also appears under certain circumstances, usually associated with bleeding. Benson believes that this color is due to porphyrins in decomposed red cells smeared on the surface, and that it does not represent a true tissue fluorescence. Other observers express themselves as convinced that there is a true red tissue fluorescence. Our observations lead us to espouse the latter point of view. We have observed, usually on the vulvas of recently (i.e., within hours or a few days at most) delivered women, two kinds of red fluorescence: (1) A bright salmon red which appears to reside in secretions arising in the glands about the clitoris, and which is occasionally smeared over the upper extremities of the labia minora and inner surfaces of the labia majora. This material can be wiped off and stains the gauze pledget employed with the same bright red fluorescent material. When this alone is present, the vulva is not regarded as showing any red fluorescence. (2) A dark brick-red fluorescence usually visible along the inner surfaces of the labia majora and outer surfaces of the labia minora. This fluorescence appears to be due to some substance residing within the tissues themselves since it cannot be wiped away nor altered by cleansing (with soap, alcohol, or ether).

It should be mentioned that in 1944 Figge and associates<sup>6,7</sup> examined the genitals of 121 women with near ultraviolet light and found a red fluorescent material in some of the cases. The red fluorescent material could usually be wiped off; some red fluorescence remained, however, and was thought to reside within the epithelial layers. The removable material was analyzed and identified. It was shown that the red fluorescence was related to the presence of porphyrins. Figge and his co-workers were interested in the possibility of a relationship between cancer and the occurrence of red fluorescent exudates. They hypothesized that porphyrins may sensitize cells to carcinogenic stimuli. The removable salmon-red fluorescent material which we observed is probably the same as that which Figge analyzed in his cases.

The foregoing are the basic observations which have been reported, in which the technique herein described, or a closely similar one, was employed. That there have been some differences in interpretations of colors is not surprising in view of the many possible variables. The human eye itself varies considerably in its ability to appreciate color. The intensity and filtration of the light have not always been identical (though they have been similar). The existence of extraneous material on the vulva may not always have been



appreciated. The degree and extent of the natural pigmentation of the vulval skin vary greatly and have often not been taken into account. (In this connection no observations made on women of the dark-skinned races are included in our own results because of the difficulties and uncertainties occasioned by heavy pigmentation.) Finally there is the variable of experience. As in other endeavors, experience is of great importance. Indeed, with so many possible variables it is remarkable that the observations reported have been as consistent as they have been. In our own endeavors three of us have checked each other countless times. When one is just beginning, one's observations are likely to be somewhat erratic, but after a short time we found that our independent observations of the same patients checked very closely. We recorded our observation of a fluorescent color with respect to both intensity and extent, on a scale of 5. For example, if only the inner one-fifth of the vulva showed a very pale purple fluorescence this was recorded as E(xtent) 1, I(ntensity) 1; if on the other hand, the whole vulva was involved with a very dark purple fluorescence, as frequently seen in pregnancy, the observation was recorded as E-5, I-5. Gradations between these extremes were recorded appropriately.

### Significance

Of great interest in connection with this phenomenon is the apparent association between purple vulval fluorescence and estrogen and/or progesterone activity. In childhood, when estrogens are absent, or so minimal in amount as to be scarcely detectable, purple vulval fluorescence is absent. From menarche to menopause it is apparent in varying intensity. Margoless describes a gradual increase in the extent and intensity of purple fluorescence during the menstrual cycle and a fading away just prior to menstruation, which parallels the known behavior of estrogen during the cycle. Benson does not believe that the variations are sufficiently distinct and consistent to permit the establishment of a precise association of this kind. My own experience does not include the daily observation of women during menstrual cycles so that I am unable to confirm or refute this point. After the menopause, purple vulval fluorescence is either patchy or absent, and this fits in with the accepted conception that estrogens exist after the cessation of menstruation, but usually in gradually declining amounts.

During normal pregnancy purple vulval fluorescence is generally more marked than at other times. Often the vulva and in particular the labia minora take on a very dark purple hue. However, there is marked variation in different individuals; some exhibit a very light purple fluorescence and others a very dark fluorescence at the same period of pregnancy. No clear-cut pattern of increase during the pregnancy and recession just prior to labor has been observed. However, within a few hours or days after delivery a progressive decrease in extent and intensity of purple fluorescence begins. This course of events has been recorded by all observers and we have established it beyond peradventure by making serial observations upon 61 women starting at the twenty-eighth week of pregnancy and continuing through labor, the puerperium, and including an observation six weeks post partum

(Fig. 1) (Singh, unpublished data). We have also made observations just prior to and immediately after delivery on 45 additional women, but of less extended nature (Omeron, unpublished data). Again the association with the established behavior of estrogen in pregnancy is notable.

The administration of estrogens to elderly women whose vulvas show no purple fluorescence, but only the greenish color previously described, is followed by the appearance of purple within 24 to 48 hours. This has been accomplished by oral estrogens, estrogens given intramuscularly, and by Premarin administered intravenously. When the estrogen is withdrawn the color fades. The accompanying tables document the fact that purple fluorescence can be produced by estrogens given to the patient parenterally or otherwise (Tables I and II).

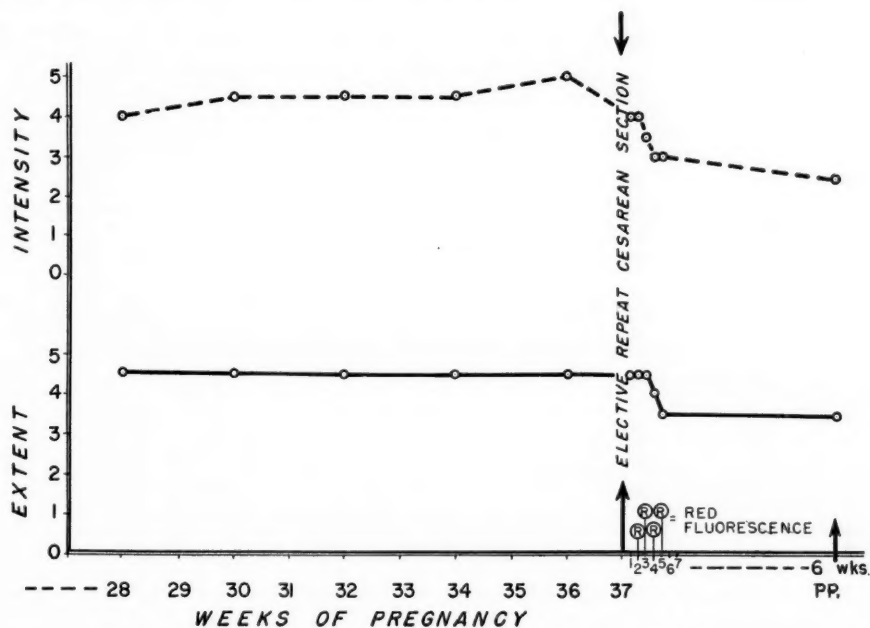


Fig. 1.—Typical pattern of observations in one of the cases included in the study.

In certain cases of threatened abortion it has been noted by Margolese, by Benson, and by Greenblatt that there is a decrease in purple fluorescence and the appearance of red fluorescence. These changes they have interpreted as due to a declining level of estrogen, and/or progesterone and as presaging abortion. If, on the administration of estrogen and/or progesterone no reversion to the normal fluorescence occurs abortion becomes inevitable in their experience, whereas if the medication results in a return to deep purple and a disappearance of the red color, the pregnancy usually continues normally. These authors regard the responses described as a method of distinguishing threatened abortion due to "endocrine" causes from abortion for other reasons.

In my own experience 35 women with threatened abortion or threatened premature labor were observed. Of these, 19 showed some red fluorescence

TABLE I. EFFECT OF INTRAVENOUS ESTROGEN\*

WOMEN OVER 60	INTRAVENOUS PREMARIN	RESULTS
4	40 mg.	4 Slight if any increase in purple after 24 hours
4	20 mg.	1 Very slight purple after 24 hours 1 No purple after 48 hours 2 No purple after 96 hours
3 (of the 4 patients shown above)	20 mg. repeated daily	
	3 doses	1 Definite purple 24 hours after second dose
	5 doses	2 Definite purple 24 hours after second dose

\*It was thought that with intravenous administration there might be an immediate effect. This was shown not to be the case so far as purple vulval fluorescence is concerned.

TABLE II. EFFECT OF INTRAMUSCULAR ESTROGEN

ELDERLY OR CASTRATE WOMEN	INTRAMUSCULAR STILBESTROL	RESULTS
5	25 mg.	4 Definite purple after 48 to 96 hours 1 Increase in purple mottling after 24 hours

In 2 of the 5 above the dose was repeated daily for several days with no further increase in purple after the initial definite response.

(Omeron, unpublished data). In several instances the red color was present without prior or immediately subsequent bleeding. Conversely, there were many with bleeding both in this series and in our group of 106 freshly delivered women who showed *no* red fluorescence, 46 of the latter group to be exact. To 6 of the patients with threatened abortion with red fluorescence, estrogens and progesterone were administered. In 5 instances the red color diminished or disappeared, in 1 case the red color increased; several weeks later this patient had placental abruption and a premature labor. Recently Margolese described 35 cases of threatened abortion in which red fluorescence made its appearance in all except 2. In 21 of the cases, the red fluorescence disappeared as a result of estrogen-progesterone administration and these pregnancies continued normally to term. In 9 of the cases in which red fluorescence persisted in spite of treatment, abortion occurred.

In certain cases of menorrhagia, unassociated with tumor, trauma, or inflammation, the uterine bleeding is associated with red fluorescence. So suggestive has this association been that both Margolese and Greenblatt believe that when red fluorescence is associated with bleeding the presumption is that the bleeding is due to "endocrine" causes (? decreased estrogenic activity). Benson objects to this interpretation on the ground that the usual patient with "idiopathic" menorrhagia has hyperplasia of the endometrium, and this he associates with *hyperestrinism*. However, so far as I know *hyperestrinism* has not been demonstrated in the usual case of endometrial hyperplasia; rather, we are dealing with prolonged unopposed (by progesterone) estrinism and the level of estrogen may be either high or low, probably most frequently the latter. It should be noted at this point that both Margolese and Greenblatt describe red fluorescence as occurring regularly at the time of menstruation.

As a generalization Margolese states that the appearance of red fluorescence signifies an actively declining estrogen and/or progesterone activity. I do not know, I have no observations which would be helpful in clarifying the matter.

### Speculations

Depending upon the cause of the phenomenon there could exist very interesting and important investigative implications. If it could be shown that purple vulval fluorescence were tied up closely with a metabolite of estrogen or even with a specific effect of a metabolite of estrogen upon certain cells or pigments of the vulval skin then it might be possible with this tool to throw some light upon the manner in which estrogens exert their characteristic local effects. If, on the other hand, it could be shown that purple vulval fluorescence were due simply to increased vascular dilatation and congestion, then the implications would not be nearly so interesting, though it would be of some value to be able to classify this phenomenon in its proper niche.

With regard to the possibility that simple congestion is the responsible factor we have made a number of pertinent observations:

1. The application of heat, both wet and dry, has not increased purple fluorescence already present, nor caused purple fluorescence to appear when none was present before.

2. The application of cold (ice) over a long enough period of time to produce marked chilling of the skin has not caused purple fluorescence to diminish.

3. The local injection of Adrenalin subcutaneously has not caused purple fluorescence to diminish. Other solutions injected subcutaneously in the area to be observed were normal saline, crystalline estradiol, and fluorescein, and none of them had any effect. The fluorescein could not be detected when injected in this manner. However, whenever it was possible to inject any of the solutions intracutaneously, which is not easy in the thin and mobile skin of the vulva, a small whitish wheal appeared against the purple fluorescent background. Fluorescein could easily be identified in such a wheal. In the case of Adrenalin, in 7 of 13 cases it appeared that actual blanching occurred in the wheal only, and in 6 instances no change occurred. These variations were probably related to the depth of penetration of the needle point. Even when every effort was made to keep the point within the epithelial layers one could never be certain that this had been accomplished.

4. Rubbing the skin vigorously to the point of abrasion produced a rather purplish area.

5. The skin over varicosities in the vulva has not appeared any different from that in other areas of the vulva.

The information so far available makes pure congestion seem an unlikely cause for purple vulval fluorescence. This is not to deny that congestion might play some role, either by adding a visible blue component, or by bringing more of a specific and significant substance to the vulva.

Actually there is a serious question whether radiations of the wave length under discussion will penetrate the entire thickness of the epithelial layers to



reach the blood vessels of the dermis. While, to my knowledge, no measurements have been made in vulval skin, it is stated that ultraviolet radiations of 3,650 Å are capable of penetrating no more than 0.1 to 1.0 mm. "of skin."<sup>8</sup> In any event, at the present time it is not possible to state definitely just where, in, on, or below the epithelium the absorbing substances lie. Yet this, of course, is a very important point to settle.

### Summary

Examination of the human vulva by means of a lamp emitting near ultraviolet light reveals:

1. No fluorescence in childhood.
2. A greenish background fluorescence, appearing about the time of puberty and continuing into old age.
3. Purple fluorescence replacing the green to varying extent and intensity during the menstrual years of life.
4. A much darker, but also variable, purple fluorescence during pregnancy, which fades rapidly at the termination of pregnancy.
5. Red fluorescence, usually but not always associated with vaginal bleeding and sometimes with impending abortion. There is both a brick-red tissue fluorescence, and a salmon-red fluorescence; the latter is emitted by secretion from glands in the region of the clitoris and is due to porphyrins.

Purple fluorescence seems to be closely associated with estrogen and/or progesterone activity. It can be produced artificially in the castrate or in elderly women by oral or parenteral estrogens. The nature of the phenomenon is not yet clear nor has the exact location of the fluorescent material been discovered. Preliminary experiments appear to demonstrate that purple vulvar fluorescence is not due to vascular congestion of the vulva per se.

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## ENDOCRINE ASPECTS OF INTERSEXUALITY

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**I**NTERSEXUALITY is a fascinating problem which has stimulated extensive medical writing. The definition of intersexuality should be simple, but indiscriminate use of the term and its synonyms has brought confusion. Since each human individual possesses male and female features in varying proportions, intersexuality is a normal condition and every human being is an intersex. In most instances it is not difficult to recognize the dominant male or female characteristics and without hesitation to classify each individual as male or female. It is possible, however, to find examples of all gradations of sex from a typical male to a typical female.

In order to consider the endocrine aspects, one must remember that a mutual interdependence of environmental, genic, and endocrine factors regulates the various degrees of sexuality. The relative importance or dominance of one of these factors varies with the species and the time of life of the individual. Inferences from animals serve to illustrate the variability. In some groups of animals and plants the production of male or female germ cells can be experimentally controlled. The oyster passes from male to female to male depending on the temperature of the water, time of hatching, and other conditions. Delayed fertilization of frog eggs results in the production of almost all or all males.

Sex is the product of sex determination, sex differentiation, and sex development. Variations may occur in any or all three of these phases.

That the sex of human beings as well as other animals is genetically conditioned is now a commonplace. The combination of genes at the time of fertilization produces a cell which possesses all the potentialities that are essential to the development of a complete individual. At the time of fertilization the genetic sex is determined. The XX combination of sex chromosomes is retained in every cell of the body throughout the life of the female and the XY combination for the male. Whatever modifications occur during development, the chromosomal pattern is retained and may be accepted as the indicator of the real sex.

Regulation of the activity within the cell is influenced by the intracellular and extracellular agents. The intracellular metabolism is complex. Any gene is influenced by other genes, not only by those of the containing chromosome, but by those in other chromosomes as well. Furthermore, chromosomes and cytoplasm interact. Add to the intracellular the extracellular or environmental factors and the possibilities for diversity become truly amazing. Is it any wonder that there are so many gradations of sexuality?

The role the endocrines play in sex determination remains obscure. Little is known about the metabolism of the germ cell. There is no direct evidence that endocrines alter chromosomes though that is a theoretic possibility. Theoretically, qualitative and quantitative aberrations of genes could account for failure to establish clear dominance of male or female determiners.

Demonstration of the sex chromosomes in the intersexes is a valuable contribution. The first studies of chromosomes in a human intersex was reported by Sevringhaus<sup>1</sup> in an individual who was living as a woman. Biopsies of the gonads, which proved to be testes, showed sex chromosomes with an X and Y component. Although the sex chromosomes were typically male, the somatic characters of the individual were a combination of male and female.

The recent report of Moore and associates<sup>2</sup> adds an interesting new approach. They found that the nature of the chromosomes in an individual may be detected by examining the epidermal nuclei in a small biopsy of skin. The sex chromosomes tend to remain compact while the autosomes are so diffuse that it is difficult to identify them individually. The XX chromosome of female cells fuse to form a mass which is sufficiently large to be readily visible. The Y chromosome is so small that it is inconspicuous. In 50 females the sex chromatin was identified in about two-thirds of the cells. It appeared as a plano-convex body lying against the nuclear membrane. In 50 male specimens they found an average of 5 per cent of the cells showing a small chromatin mass at the nuclear membrane.

In a skin biopsy, taken at the age of 14 months, from a female pseudohermaphrodite with adrenogenital syndrome, sex chromatin was demonstrated in 75 per cent of the cells. The chromatin masses were identical with those of the typical females. A probably male pseudohermaphrodite at the age of 24 years had a skin biopsy which showed a small chromatin mass in only 4 per cent of the cells.

To investigate whether the morphology of the sex chromatin is influenced by sex hormones they were able to demonstrate a sex difference in nuclear morphology in cat embryos before the stage of gonadal differentiation. They were unable to alter the sex chromatin in neurons of the cat by orchiectomy or oophorectomy in early life or by administration of the opposite sex hormones to such animals. They believe that the sex chromatin is a stable component of the nucleus whose morphology is not influenced by sex hormones and that the sex chromatin is a reliable indicator of chromosomal sex in hermaphrodites.

Moore and collaborators invited a general use of their method which they published in detail. It is hoped that a large number of intersexes will be studied in this manner. If their results are confirmed, a valuable contribution to the classification of the intersexes has been made.

We were able to confirm their findings in a female with adrenogenital syndrome. A biopsy of skin from this patient was examined by Dr. Rebeck, Associate in the Department of Pathology at the Henry Ford Hospital, who made a photomicrograph (Fig. 1) which is similar to those published by Moore and his associates. Other biopsies from intersexes are under investigation.

Some of these are easily classified while others are difficult to interpret. I hope that more experience will clarify the problem and justify the reliability of the method. It would be most fortunate if the real chromosomal sex could be determined in all intersexes.

Sex differentiation, partly genetic and partly endocrine, deals with the origin and differentiation of the male or female form of the rudiments of all sex characters. The rudiments appear first in a generalized form and subsequently they acquire specific characteristics peculiar to the sex. Genes and endocrines serve merely as regulators of this attainment.

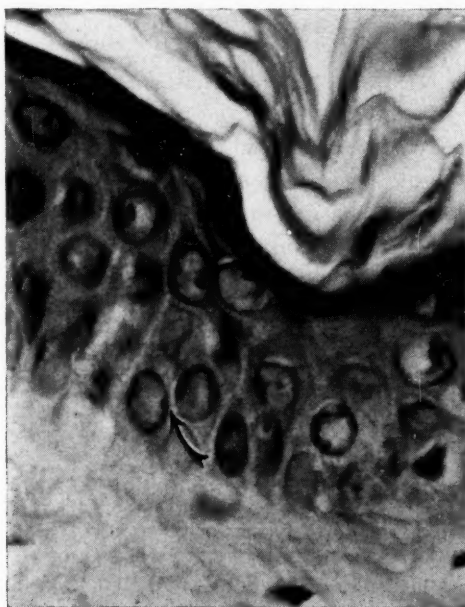


Fig. 1.—Photomicrograph of epidermis of patient with female adrenogenital syndrome. Arrow points to chromatin mass in nucleus.

In early embryonic life genic regulation continues. Cells are grouped and regrouped. As growth proceeds organizers serve as the intermediary mechanism between the genic equipment and the final form and properties of the developed individual.

The concepts of the nature and manner of action of the organizers have been reviewed by Needham<sup>3</sup> in his book, *Biochemistry and Morphogenesis*. A large array of experiments establish the existence of organizers and demonstrate their chemical nature. They are referred to as morphogenetic hormones.

If the region of the dorsal lip of the blastopore is grafted into another embryo in very early embryonic life (blastula or gastrula stage) a secondary embryo will be formed. The graft is the organizer which may be defined as a living part of an embryo which exerts a morphogenetic stimulus upon another part or parts, bringing about their determination. The chemical substance emitted by the organizer is an evocator. An inductor may be living or dead tissue, a chemical fraction or a chemical substance of known constitution which carries out an induction similar to that of an organizer.



The state of the reacting tissue is just as important as the stimuli. The state of reactivity is known as competence. The presence of competence and the presence of capacity to react to a stimulus occupy different time spans of the developmental life of the embryos. Competence and organizers do not arise and disappear at the same time. Competence appears for only a relatively short time. The organizer seems to begin before and persist for a long time afterward.

Biochemistry of the organizer has attracted wide attention of many workers. The results of their experiments have been reported by Needham.<sup>3</sup> Some of the findings are worthy of mention here because of the importance of steroids which were demonstrated to be inductors.

Crushing the cells of the organizer had little or no deleterious effect on their inducing activity. They were resistant to heat and could be boiled for some time without loss of activity which excluded enzyme effects. It was evident that the morphogenetic stimulus of development of the life of the cell, in just the same way as the hormones of any endocrine gland, is separable from the life of the glands. The stimulating activity was not lost by preserving in alcohol for months, nor by treating with xylol, paraffin, hydrochloric acid, or ether. Furthermore, these treatments when applied to noninductors, conferred activity on them. The activity of the noninductors, however, was less. Absence of species specificity was noted. Even adult tissues of many animals were effective stimulators. No specific difference could be established between the different tissues of different phyla.

Neural inductions can be brought about by a wide variety of chemical fractions and pure or relatively pure substances. Which of these, if any, are identical with the evocator upon which the whole normal process of development depends, remains unanswered. Some of the studies, however, suggest that the natural evocator is a steroid substance. The relationship between the steroids essential at so early a level in embryonic life and the endocrines later offers an interesting field for speculation.

Development is fundamentally a progressive restriction of fates. It is a continual closing of doors. The earlier in embryonic life an aberration occurs the more profound the deviation will appear when development is complete. On account of the far-reaching effects on sex formation when adverse influences operate before differentiation of the gonads, intersexes originating at this level are called constitutional.

Until the fifth to the seventh week each embryo has the basic source of material for any part of the male or female equipment. As development proceeds the indifferent gonad becomes a testis in the male or an ovary in the female and the reproductive tract, the external genitals, and other sexual characters correspond. The assumption that sex differentiation depends upon the endocrine secretion from the embryonic gonad arose from the studies of Lillie<sup>4</sup> on the freemartin reported in 1917.

The freemartin is the female of a male-female pair of twins in cows. Fusion of the chorion and blood vessels permits the passage of blood from one twin

to the other. Under these conditions the male develops typically while the female is modified. The reproductive system assumes the male type except the external genitals which are largely female. It is not capable of reproduction. Similar conditions were found in a few instances in the pig. No other animal has responded in a similar manner.

Moore,<sup>5</sup> over a period of years, attempted to duplicate the freemartin condition in other animals. Before estrogen and androgen were available, transplants, grafts, and parabiosis were studied. When hormones became available they were used in a variety of ways. Some of Moore's conclusions are noteworthy. He found no evidence in any vertebrate that hormones are secreted by the developing gonads during the period when the embryonic duct system undergoes modification in the definitive male or female type. In the chick and opossum, gonads did not respond to gonadotropin until after differentiation of male or female type or system. Hormone secretion by gonads apparently begins in the chick shortly after hatching, in the rodent about at birth, and in mammals in late embryonic life but probably too late to act on the fetus.

Ovarian agenesis illustrates the capability of the reproductive tract and external genitals to develop entirely independently of the gonads. During the last decade a number of these anomalies have been reported with more or less complete hormonal studies. Other developmental anomalies are usually associated. The nipples, breasts, labia, vagina, and uterus are well formed but usually infantile. Hair develops on the labia, pubis, and axillae but not until the average age of puberty. The clitoris is not enlarged. The ovaries are a mere strip of stromal tissue without germ cells. Gonadotrophic activity of the pituitary is increased as evidenced by increased secretion of FSH. Wilkins<sup>6</sup> reported an average titer of 192-576 M. U. per day. The youngest patient in whom he found FSH above normal level was 12 years old. The elevation of FSH appears at the age when pituitary gonadotropin first appears. The 17-ketosteroids average 3 to 6 mg. per day.

Normal female differentiation of the genital structures in patients who do not have ovaries is excellent clinical confirmation of the genetic theory of sex determination. While these patients are not strictly intersexes they belong to the same pattern of mechanism of sexual differentiation.

The adrenogenital syndrome offers another approach to the problems of sexuality. In early embryonic life the adrenal gland is larger than the kidney, at 8 weeks equal in size, and at birth one-third as large. The adrenal gland is proportionately larger at birth than at any time thereafter. The adult gland forms 0.01 per cent of the entire body weight while at birth it is 0.2 per cent. The large X or androgenic zone accounts for the relatively large size at birth.

The close association of gonads and adrenal cortex is emphasized by deVaal.<sup>7</sup> He assumes that it could be possible that the cells migrate from one into the other. Since both glands subsequently produce steroids, the two glands together might be considered as forming the steroid apparatus. He further proposes the term "species gland" to include the adrenals and the

gonads since they are essential to the preservation of the species. The concept is physiologic and not anatomic.

Intersexuality according to his view is due to a disturbance of development of that combination of gonad and adrenal cortex designated as the species gland. The entire chromosomal configuration of the zygote is made responsible for the disturbed organogenesis of the gonad (and possibly other genital organs) and the adrenal cortex. It has not been possible to prove the influence of androgenic substance from the mother so that the idea of induction of intersexuality through androgenic substances of maternal origin remains speculative.

Excessive production of adrenal androgen in the fetus results in female pseudohermaphroditism so well described by Young.<sup>8</sup> It is associated with adrenal hyperplasia. Ovaries and the Müllerian duct system develop and the Wolffian ducts disappear. The vagina communicates with the urethra and a urogenital sinus persists. This deviation should occur around the third or fourth month before normal urethral and vaginal relationships are attained. After birth excessive secretion of androgen continues. The 17-ketosteroids are always increased in relation to the age of the patient.

Intersexes with testes or ovotestes instead of ovaries who have genitals similar to those in congenital adrenal hyperplasia have low 17-ketosteroids. They do not have other manifestations of hyperplasia of the adrenals, such as secondary male characters before puberty. The origin of their deviation is of a more complex nature.

Treatment of patients with adrenogenital syndrome is disappointing. If one of the adrenal glands is removed the remaining gland maintains the excessive secretion. Young<sup>8</sup> removed as much as one and one-half of the glands without controlling virilization. Wilkins<sup>6</sup> reported the suppression of 17-ketosteroids by the administration of cortisone. Evans and Riley<sup>9</sup> report the use of cortisone in 4 patients with adrenocortical hyperplasia. In one of their patients one and two-thirds of the adrenals had been removed with temporary depression of the 17-ketosteroids. Throughout 18 months of treatment with cortisone the 17-ketosteroids remained above normal. Interruption of treatment was followed by increased steroid. In two of the patients cortisone treatment was attended by a slight breast development and decreased acne. Estrogens were within normal levels.

Hormone assays are an important part of their investigation. Their report of 12 male and 18 female pseudohermaphrodites may be taken as representative of that field. In 5 male pseudohermaphrodites the rate of 17-ketosteroid excretion was within or slightly above the normal female range. In 4 adults, 2 had normal estrogen excretion and 2 were subnormal. The FSH excretion rate was at normal adult female level and 1 was abnormally high related to low estrogen. In the female pseudohermaphrodites the 17-ketosteroid excretion rate was increased in all but one in whom it was in the low normal level. In all of those whose 17-ketosteroid rate was elevated the estrogen ex-

cretion was excessive or within normal range. Alpha and beta fractionation of the 17-ketosteroids in 4 patients showed a small beta fraction. This indicated adrenal hyperplasia rather than cortical tumor.

To be limited to estimation of the quantity and quality of hormones excreted is tantalizing. What one would really like to know is the native hormone of each gland and how it is metabolized and utilized. There is further limitation to postnatal life because the hormones of the embryo and fetus are quite inaccessible.

Genes and endocrines are alike in serving merely as regulators. In 1939, Danforth<sup>10</sup> wrote, "Preoccupation with problems relating to the source, action and purification and assay of hormones and vitamins has led to a conspicuous neglect of some other aspect of their biological significance." "Existing information does not justify a tendency, prevalent in medical circles and the press, to regard the hormones as definitely apart from other biological phenomena and characterized by a kind of creative potency of their own." I wonder if the present-day attitude has changed materially.

Exploration of the etiology of the intersexes has not yielded a value for the endocrines at all comparable with their use in treatment. The great variety of forms in which intersexuality may appear in man makes it impossible to give a definite scheme for rational therapy. It will be necessary to judge each case on its individual features. These unfortunate beings are sick people and they deserve sympathy and understanding. They are to be treated with all the resources of the art and science of medicine.

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## CLASSIFYING OVARIAN TUMORS

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WHEN the editors of this distinguished JOURNAL generously asked me to participate in a tribute to Dr. George Kosmak, on the occasion of his eighty-first birthday and his retirement as senior editor, they suggested my preparing a brief analysis of the development of the modern classifications of ovarian tumors. The opportunity to pay homage to an old and esteemed friend, whose untiring efforts to create a great JOURNAL have been so fruitful, seemed worth risking the struggle with a subject manifestly beset with contradictions and full of lofty conjectures and yet not overly important in its practical significance. Although familiar with the subject, I found it not too simple to crowd an unwieldy mass of information onto a few pages and still succeed in presenting a reasonably clear analysis of the factors which are responsible for the considerable diversity and multiplicity in the current classifications of ovarian tumors.

During the thirty years of Dr. Kosmak's editorial activities some seventy-five or more classifications of ovarian tumors have appeared in textbooks, monographs, and medical journals. That no two are quite alike may seem strange on first glance but, in fact, is not, because opinions on how to classify differ considerably. The clinically minded demand a serviceable scheme principally based on easily discernible morphologic and symptomatic characteristics which will be useful as a guide to clinical diagnosis. The academically minded, who frown upon clinical classifications as outmoded, insist upon strict adherence to histogenic criteria as the proper scientific approach. The middle-of-the-road adherents attempt to reconcile this schism by adopting some of the criteria of both schemes, albeit not very successfully, and still some others have chosen to abandon all orthodox methods in favor of simple listing of known varieties of ovarian tumors as recommended by the late James Ewing. During the last twenty years, however, the histogenic approach has become the favored scheme and although logical in principle, as originally proposed by Waldeyer and Pfannenstiel, by virtue of the discovery of many ovarian tumors since then, has been confronted with intangibles which put the scheme into a highly conjectural state.

Ordinarily, the cellular structures and patterns of neoplasms closely resemble those of the adult organ in which they originate and, hence, histogenic relations are readily ascertainable. This explains why tumor classifications, in general, have reached a satisfactory degree of uniformity and are universally accepted as sound. The reverse applies to ovarian tumors which in

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their histologic details do not often resemble the cellular patterns of the mature gonad and only remotely resemble those of its embryonal antecedents. The accurate determination of histogenic relations between tumor and parent organ is still, therefore, largely a matter of conjecture and this in spite of the illuminating contributions to the embryology of the ovary by Fischel, Felix, Robert Meyer, Varangot, Akagi, and others. Of theories about the histogenesis of tumors there are many, ranging from faulty differentiations of the mesenchyme to prosoplasia of surface and tubular elements of the parenchyma, and from heterotopic inclusions of nonovarian elements to dysontogenetic deviations in the development of primordial follicles. Some of them go back many years, like the hydrops folliculi theory of Meckel, which attempted to explain the origin of ovarian cysts on the basis of hydropic degeneration of primordial follicles; or the theory supported by such great pathologists as Rokitansky and Virchow, who considered it probable that all ovarian cysts were derived from solid tumors by some mysterious process of collagenous degeneration followed by a prosoplasia of fibrocellular elements into epithelial structures. Some of these theories may seem strange to us now, but students of ovarian oncology know that they continue to creep up in some disguise, like the genesis of pseudomucinous cysts from Brenner tumors. What has been alluded to here, all too briefly, has been discussed exhaustively in the distant past by Waldeyer, Olshausen, Pozzi, and Pfannenstiel, and in the more recent decades by Sternberg, Geist, Kermauner, Walter Schiller, Robert Meyer, Emil Novak, Howard Taylor, Jr., Ewing, Barzilai, Spencer and Reel, Ricci, Josephine Barnes, Kottmeier, Teilum, Robert Crossen, and a number of others among the many who have attempted to design classifications. Suffice it to say that no classification so far has met with universal approval and the steady procession of new schemes testifies to the truth of this statement. There are still those who contend that the time-honored clinical classification, as proposed by Olshausen and modified by Pozzi, is indispensable to clinical diagnosis as recently discussed by Conill, Ricci, and Crossen. Goodall, Howard Taylor, Jr., Walter Schiller, Robert Meyer, and Teilum have proposed ideal histogenic classifications, some simple and some, like Goodall's and Meyer's, quite complicated and meant primarily for academic purposes. Some authors have advocated abandoning special groups for malignant tumors on the assumption that every ovarian tumor has its malignant variety, and others like Meigs have done the exact opposite by providing a subdivision for unclassifiable varieties. A considerable group of classifiers have adhered more closely to histologic than to histogenic criteria because of the vagaries attaching to the latter, in particular Howell, Anspach, Meigs, Faulkner and Douglass, Counseller and Broders, Wharton, and Ricci. Those that have been content with the plain listing of tumors, as Ewing, Brewer, Fulkerson, and Curtis and Huffman without attempting to follow any orthodox approach probably did so for the same reason.

In the light of these conflicting ideas on how to classify ovarian tumors it is disturbingly evident that we have not come very far since Stephen Howell said in 1888 that the classification of ovarian tumors is purely arbitrary

since it may be based on any of various features and that "just as from the Scriptures evidence may be adduced in support of any special religious doctrine, so even preconceived opinions concerning ovarian pathology may seemingly, at least, be upheld by phenomena observed in this glandular complex."

Ovarian tumor classifications were simple prior to 1900 because of the relatively small number of tumors to be considered. From then on the problem has become progressively more difficult for, as Graves said so appropriately in 1928, "every little while there is discovered in the constellation of ovarian neoplasms a new tumor that adds fresh trouble to the difficulties of classification. The extraordinary versatility of the ovary in tumor formation is attested by the fact that thirty or forty varieties have already been described.\* Histogenesis in its broader sense is the essential basis for all tumor classifications, but in the entire galaxy of ovarian growths not more than one or two have an undisputed ancestry. Moreover, from the clinical exigencies of the case other factors than histogenesis cannot be avoided, such as morphology, clinical behavior, malignant properties, chemistry of contents and relationship to tumors of other organs. It is clear then that whatever classification is made must be one of expediency and not one of scientific accuracy." Both Howell and Graves were astute thinkers, one an outstanding pathologist and the other a most accomplished gynecologist versed equally well in the embryology, anatomy, and pathology of the ovary; each designed an excellent classification for his time and yet their reactions to the problem, *though forty years apart*, certainly are the same in essence. How much further have we come since Graves expressed his thoughts?

In the last twenty-five years ovarian tumors, formerly considered rare, have increased in number and types and have added to the already existing difficulties by defying, at times, not only identification but classification even in the hands of accomplished and experienced diagnosticians of ovarian pathology. The last report of the Committee on Ovarian Tumor Registry of the American Gynecological Society testifies to this, for, among the 720 tumor preparations listed, which made the complete circuit of the committee, 79 appear on the list as "unclassified." When experts cannot agree, particularly such outstanding experts as Novak, Faulkner, Gardner, Martzloff, and Traut, the problem of classifying must still be far away from a solution. This becomes even more apparent when one compares the grouping of tumors in the many classifications devised in the last thirty years. I have singled out granulosa-cell tumors because of their increasingly significant position in the galaxy of ovarian neoplasms. A perusal of the various group designations given in Table I should suffice to impress the reader with the difficulties yet to be conquered.

There are numerous other instances which illustrate the existing divergencies in opinion over grouping of ovarian tumors. For instance, Sternberg grouped granulosa-cell tumors with cystadenomas and Brenner tumors, to which Anspach later added arrhenoblastomas and endometriomas. Robert

\*Meigs listed over 100 items in 1934.

Meyer, admittedly one of the best-versed gynecologic pathologists, considered it histogenically correct to group pseudomucinous cystadenoma with dermoids under teratomas. Schiller grouped this same tumor with endometrioma and serous cystadenoma, assuming them to be heterotopic derivatives in a Müllerian direction, a theory originally propounded by Kossmann in 1894. Schiller also fitted arrhenoblastoma and disgerminoma into this group, but classed granulosa-cell tumors with fibromas and thecomas as ovario-genic derivatives. Goodall, who designed one of the earliest modern histogenic classifications, grouped granulosa-cell tumors with hydrops folliculi and corpus luteum cysts. Counsellor and Broders classed dermoids with follicle cysts and Meigs put granulosa-cell tumors in with the solid parenchymatous tumors but grouped arrhenoblastoma, dysgerminoma, and hypernephroma with dermoid cysts under embryonal derivatives. The number of similar instances of divergent attitudes toward histogenic grouping are many more than space permits me to quote.

TABLE I. GROUP DESIGNATIONS FOR GRANULOSA-CELL TUMORS IN 26 CLASSIFICATIONS\*

NO.	YEAR	AUTHOR	GROUP DESIGNATION
1	1926	Sternberg	Mature epithelial neoplasms
2	1928	Graves	Proliferating tumors
3	1929	Fulkerson	Carcinoma
4	1931	Blair Bell	Lepidomata
5	1933	Goodall	Graafian follicle derivatives
6	1934	Anspach	Benign epithelial tumors
7	1934	C. Jeff Miller	Embryomata
8	1934	Joe V. Meigs	Solid benign parenchymatous tumors Solid malignant parenchymatous tumors
9	1936	Conill	Hormonal tumors
10	1937	Counsellor and Broders	Tumors of questionable origin
11	1940	H. Taylor, Jr.	Tumors arising from specific cells of the gonad
12	1941	Crossen and Crossen	Undifferentiated sex cells
13	1942	Geist	Benign neoplastic parenchymal tumors
14	1946	Robert Meyer	Tumors arising from ovarian blastoma
15	1946	Neuweiler	Epithelial tumors
16	1946	Scott and Van Wyck	Special ovarian tumors secreting hormones
17	1947	Wharton	Epithelial rests
18	1947	Spencer and Reel	Ovario-genetic tumors from fetal cell remnants
19	1948	Walter Schiller	Ovario-genic true tumors
20	1948	Ricci	Malignant solid tumors
21	1949	Josephine Barnes	Tumors associated with endocrine dysfunction
22	1949	Faulkner and Douglass	Embryologic rests
23	1952	Emil Novak	Malignant solid tumors (embryonic or dysonto-genetic)
24	1952	Kottmeier	Tumors with endocrine function
25	1952	Teilum	Granulosa-cell tumor group
26	1953	R. Crossen	Malignant tumors from ovarian mesenchyme

\*Group designations appearing in the above table have been used by other classifiers of ovarian tumors. The list is by no means complete, but since the variants are not significant they have been omitted for the sake of clarity. Novak's designation "feminizing mesenchymoma" is not used in his classification.

Terminology, likewise, has added its share to the existing confusion but to a lesser degree, for the naming of tumors is rapidly approaching uniformity. Variations in designations of individual tumors are of minor importance and their spelling matters even less. For instance, what does it matter whether to spell disgerminoma with an *i* or a *y* as long as we remember that Meyer used the prefix "dis" to denote a negative force while "dys" indicates something



bad or untoward. Schiller read into Meyer's use of "dis" the meaning of a bilateral origin from gonad or germinal cells as contrasted with "dys" to mean "wrong." This, as Meyer so aptly put it in his autobiography, is just another "querelle allemande," for in either instance the term denotes the histogenesis of the tumor.

Then there is the naming of granulosa-cell-type tumors. Should they be called just that, as a number of the more recent classifiers have done, or should they be designated as granulosa-cell carcinoma, as proposed by Novak? The answer hinges upon the intent on how to use the term. The simple term "granulosa-cell tumor" is a histologic rather than a histogenic designation which does not denote its growth behavior nor its function. Novak's "granulosa-cell carcinoma" does the latter but in this respect is overinclusive since the majority in this class of tumors are clinically benign. Novak's latest proposal to class them as "feminizing mesenchymomas" together with thecomas and luteomas (whose existence was disputed by Robert Meyer) aims in the right direction, albeit that some of them are not clinically feminizing. But where shall we place gynandroblastoma? Novak classes this tumor with granulosa-cell tumor, thecoma, arrhenoblastoma, and dysgerminoma as embryonic or dysontogenetic tumors, while Gunnar Teilum classes it by itself, just as he sharply separates the feminizing from the masculinizing tumors, which in his classification include arrhenoblastomas, Leydig-cell, hilus-cell, Sertoli-cell, and adrenal-cell tumors, luteoma, masculinovoblastoma, and folliculaoma lipidique of Lecène, although the latter, just as luteoma and Leydig-cell tumor, is not always masculinizing, and masculinovoblastoma may not be accompanied by hormonal manifestations. So far, nobody has offered the proper solution to classifying tumors capable of producing hormones, unless it be on a clinical basis. If we wish to be academic and adhere strictly to histogenic criteria, we should create a separate category for virilizing hypernephromas which most probably are heterotopic while most other virilizing tumors are mesenchymal in origin. There are many such queries still unanswered, even such simple ones as the correct use of cysts, cystadenoma, adenocystoma, and cystoma which are morphologic terms. Meyer's proposal to add the suffix "blastoma" to cysts of neoplastic origin to denote their genesis, has been accepted by several of the European classifiers but has not become popular in this country. In puzzling over these questions, I was reminded of Haldane's classical remark that "only evil can come from forgetting that man must be considered from many angles," and there I shall let the matter rest lest I add to the confusion.

In view of these many conjectural propositions, are we then justified in insisting that only histogenesis can give us the correct answer to classifying tumors? I doubt it. Histologic classifications, such as Howell proposed, or Ewing used in a more extended but less formal manner, undeniably are important guides to pathologic diagnosis. A histogenic classification, if accepted as conjectural at this stage of knowledge, is interesting and intriguing but hardly more significant than the histologic grouping of tumors. Neither is of material help to the practicing physician who, understandably, is less

interested in a highly academic controversy than in some simple guide to clinical diagnosis. Concerning histogenic classifications, a common understanding can be reached only when all students of the histopathology of ovarian tumors have agreed not only on common descriptive terms for confusing cell patterns but also on a better system of grouping tumors. Needless to say that, although we have learned something about tumorigenesis from experimentation, the so-called desmoplastic cancer cell can trouble the diagnostician just as sorely as does the so-called fibroepithelial cell, and pathologists still have considerable difficulty at times in making up their minds over what they have to deal with, for their final decision is not necessarily based on sound criteria but on individual leanings, as proved by subsequent clinical events. Anybody having studied ovarian tumors over long periods of time must be tempted to throw out all elaborate classifications and return to the very simplest grouping. As matters stand, I see no conflict in retaining a simple clinical classification based on morphology and symptomatology for the practitioner's daily need and a mutually satisfactory histogenic or histologic system for academic purposes and to serve as a laboratory guide.

Before bringing the subject to a close, a word must be said about including nonneoplastic tumors in our modern classifications. This, again, to some degree is a matter of attitude. The word "tumor" signifies any enlargement persisting abnormally long. On that basis all nonneoplastic enlargements, regardless of their origin, should be included for the sake of differential diagnosis for clinical as well as laboratory purposes. If the word "tumor" is to indicate neoplasia, as is done loosely in medical parlance, then nonneoplastic structures should not be listed, as done by many classifiers, but to clarify the intent such classifications should be titled accordingly.

To summarize then, there are various ways of classifying ovarian tumors as can be readily learned from a comparative analysis of the many classifications proposed in the past. All have their merits though some are more practical than others. How to approach the problem is all a matter of attitude, just as it is a matter of personal leaning toward one or the other in choosing the one most congenial for teaching purposes. Man's habit of classifying is an acquired discipline which stems from his inherent addiction to collecting everything from things to thoughts. He just cannot resist the temptation to bring matters of a similar nature under one single system of laws, always hoping that once placed there, they are there to stay. When man fails in his quest, it is because he attempts to bridge the gap between conjecture and reality with analogies and oversimplification of complicated processes, which later generations of investigators are prone to feed into the humorless mills of minute criticism that have no ear for subtleties nor any patience with abstractions. What can be done with the yield depends entirely upon the ability of other generations to avoid the pitfalls of their predecessors, for intangibles will continue to creep up. On the whole, this leveling process spells progress in the right direction, although not every change necessarily is for the better and, at times, is hardly of more significance than the ass's kick at the dead lion. It was in some such manner that the

classifications of ovarian tumors came into existence, were modified, and in due course have multiplied until now their usefulness is threatened by the sheer weight of their numbers. Which one to select for one's own use remains a matter of individual leaning toward one system or another. The thing to remember is that each one was designed in the hope of improving matters in line with advancing knowledge. That final perfection has not been reached is right in line with every other development in science, for knowledge is a moving quantity. The foregoing comments were written in praise of man's courage to persist in his quest to search out truth and not in a spirit of criticism of his imperfections.

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2000 VAN NESS AVENUE



## CLINICAL AND EXPERIMENTAL ENDOMETRIOSIS

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IT IS a great pleasure and honor to be among the contributors to the Festschrift number of our JOURNAL in honor of Dr. George W. Kosmak's eightieth birthday. It is especially pleasant to have the opportunity of discussing the subject of "endometriosis." During Dr. Kosmak's able editorship, many of Sampson's<sup>1</sup> brilliant articles on endometriosis appeared in the JOURNAL. The beautiful colored plates accompanying these early observations are permanent testimony not only to the pre-eminence of the author but to Dr. Kosmak's editorial judgment and vision for the JOURNAL of the future.

Observations concerning endometriosis appearing in the literature previous to 1921 did not receive the attention which their careful reporting deserved. The classic descriptions of adenomyosis and adenomyomas by Cullen<sup>2</sup> in 1896 and in 1908 should at once have directed the attention of clinicians and experimentalists to this important clinical condition. The description of chocolate cysts by Pick<sup>3</sup> in 1905 should have indicated the need to gynecologists and pathologists for a more critical study of similar lesions. Sampson's<sup>1</sup> observations, beginning in 1921 and extending through the remaining twenty-five years of his life, for the most part either directly concerned endometriosis, or in some way were directed toward proof of his theory concerning its etiology.<sup>1c</sup> His classic primary observations and his subsequent additions to the theory which he proposed marked one of the milestones in gynecology and provided a shining example of the value of painstaking clinical research. Sampson's theory of the dissemination of these important lesions still dominates today's thinking as well as the diagnosis, physiology, and treatment of this crippling condition.

The fundamental assumption of Sampson's theory on the etiology of endometriosis is expressed in the title of one of his later papers,<sup>11</sup> "Peritoneal Endometriosis Due to the Menstrual Dissemination of Endometrial Tissue Into the Peritoneal Cavity." His primary concept concerning the viability of endometrial bits cast off during menstruation has not yet been proved although many workers have made attempts to do so. Further study of the widespread distribution of endometriosis in the human being led Sampson to believe that additional paths of transport, such as blood and lymph vessels, carried this viable transplantable tissue to distant portions of the body.<sup>1h, 1k</sup> Recently Javert,<sup>4</sup> in several convincing articles based on the accumulated facts and histological evidence from the literature and from his own surgical specimens, assumed that the endometrial tissue observed in resected lymph nodes was

transported from the uterine cavity via lymph vessels in a similar manner to that which we have accepted for the spread of adenocarcinoma of the uterine corpus.<sup>1c, 1g, 5, 6, 14, 15, 16b</sup> Javert speaks of this as the theory of "benign metastasis." He presents several examples of endometrial bits trapped on their path of transport in the lymph nodes and spaces as well as in the lumen of the Fallopian tubes. He mentions one node that contained a typical although small endometrial cyst. Sampson and others had previously drawn a similar analogy. Sampson repeatedly asserted that proof of the viability of endometrium cast off during menstruation was necessary before these theories of transplantation could be fully accepted.

The vast majority of the large number of clinical reports dealing with endometriosis have largely been concerned with the incidence, detection, distribution, and treatment of this disease. Ranney<sup>34</sup> in 1948 in a comprehensive review has collected the essential details, both clinical and experimental, that have a direct bearing on the problems concerning the etiology of endometriosis. These articles, ranging from suggestive case reports to extensive material culled from large series and carefully correlated with histological study, have added materially to the recognition and our present conservative concepts in treatment. The fundamental origin of this functioning tissue and how it arrived in its ectopic location will probably be proved only by tissue culture or experimental work in the animal laboratory.

The fundamental and continued experiments of the surgical transplantation of endometrium from the uterine cavity to distant locations in the same animal are almost universally successful. The viability of these transplants, their vascularization, surrounding tissue reaction, and physiological responses, are now quite well established. The earlier experiments in transplantation were done principally on nonmenstruating animals. These results therefore cannot be as conclusive as those studies done recently in the higher groups of menstruating mammals. Although the pelvic anatomy in the Rhesus monkey is slightly different from that of the human being, the physiology of the reproductive organs is almost identical. This type of animal therefore lends itself ideally to experimental investigation of all those factors which may parallel the development of endometriosis in the human female.

We wish in this presentation to review that portion of the work already in the literature as a framework for our interpretations based upon twenty-five years of clinical and experimental interest in endometriosis.<sup>10</sup> Our experimental observations for the past nine years have been confined primarily to those in two separate groups of Rhesus monkeys (*Macaca mulata*).

We also wish to add two of our most thought-provoking human surgical specimens (Figs. 6 and 7).

### Transplantation

Stilling<sup>7</sup> in 1910, working with rabbits, reported consistent "takes" of endometrium, vagina, and uterus, when transplanted into the spleen. Jacobson<sup>8</sup> confirmed these observations and later using monkeys found that survival of the implant was not as constant, but that the bleeding which occurred

in the transplanted endometrium in one animal was similar to that seen in women. Hesselberg, Kerwin, and Loeb,<sup>9</sup> using guinea pigs, successfully transplanted kidney, thyroid, myometrium, and endometrium. These observers found that about three days after implantation the cells which had become necrotic regenerated and, at the end of five days, firm attachment to the host had occurred. This observation has been further verified by the work of Hartman<sup>18</sup> in monkeys in which experimental endometriosis was produced.

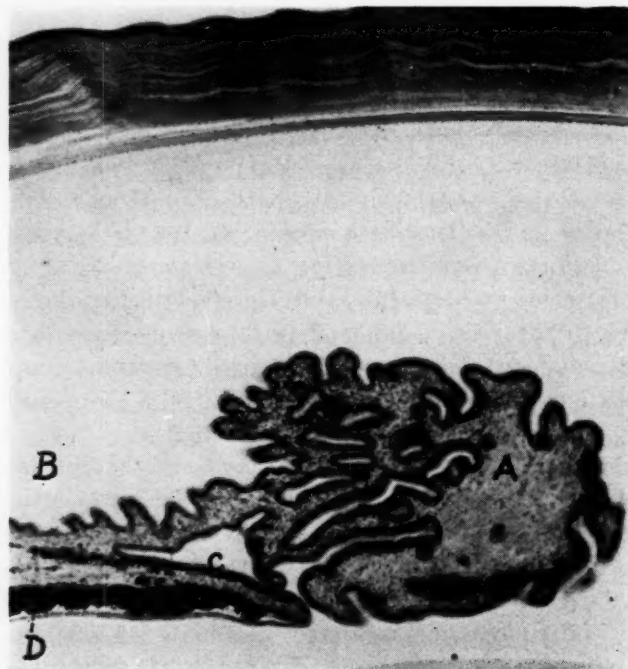


Fig. 1.—Bit of endometrium (A) excised from the uterus, which has been implanted into the anterior chamber (B) of the rabbit's eye, the epithelium and stroma (C) extruding through the pupil to the undersurface of the iris (D).

Bykow<sup>17</sup> concluded after transplanting the entire uterus to the omentum in dogs that the endometrium has greater proliferative tendencies than does the myometrium. O'Keefe and Crossen<sup>22</sup> noticed the dense adhesions that were produced by transplantation of endometrium to the appendiceal region in dogs. We wonder if in the clinical, early gross lesions of external endometriosis, the superficial peritoneal fibrinlike adhesions may not be of considerable importance in the primary development of the endometrial lesion and its subsequent widespread dissemination. We will consider in our discussion and illustrate (Fig. 16) this type of adhesions as they appeared in our experimental animals.

In 1928<sup>10a, b</sup> and 1932,<sup>10c</sup> the senior author reported an experimental study of autologous transplantation of surgically excised bits of endometrium into the anterior chamber of the rabbit's eye (Fig. 1). This transplantation was regularly successful and vascularization of the implant seemed to occur within twenty-four to forty-eight hours (Fig. 2).

The appearance of the "blush and blanch" phenomena studied so extensively by Markee<sup>11</sup> formed the basis of our conclusions. These experiments also indicated that the endometrial epithelium retained its viability and the power of proliferation by extending through the pupil to the inner surface of the iris (Fig. 3). Furthermore, it seemed that this proliferated epithelium either carried with it typical endometrial stroma or was capable of evoking a stromal response that was unlike the local connective tissue of the normal iris (Fig. 3). Fig. 4 also suggests the added power of epithelial invasion into the stroma of the iris. We do not believe that this epithelial proliferation is similar to that which commonly complicates surgical procedures on the human eye.

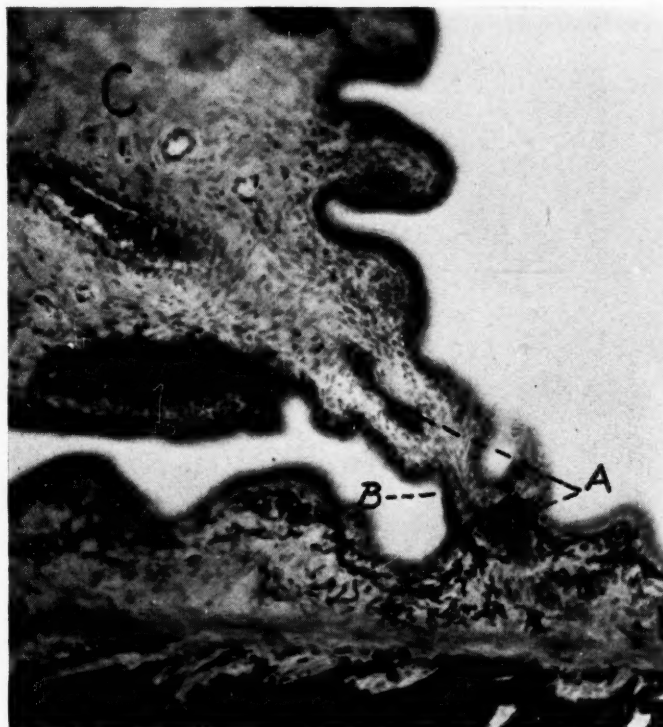


Fig. 2.—Course of an artery (A) extending from the iridal vessels, through the stalk (B) to the substance of the implant (C).

Based on this important evidence, we may be justified in concluding that adenomyosis is probably a similar proliferative and invasive process. In his early classical descriptions of adenomyosis, Cullen<sup>2b</sup> by means of serial sections traced this outward growth from the basal layer of endometrium to the serosa of the uterus. Frankl<sup>35</sup> believed that stromal cells may act as "endometriogenetic islands" for the later appearance of the glandular epithelium in adenomyosis. Papanicolaou<sup>36</sup> verified this heteroplasia from stromal to epithelial-type cells in studies of the endometrium of guinea pigs. Te Linde and Scott<sup>12</sup> believed that internal and external endometriosis are the result of different etiological factors. We, however, from our clinical and these experimental observations have the distinct impression that although geographically their locations are different, the etiology is fundamentally the same.



### Heteroplasia

In some instances portions of the previously mentioned proliferated endometrial epithelium in the rabbit's eye appeared to have assumed the histological characteristics of tubal epithelium. This transition in epithelial-cell type may have been produced by the environmental changes and/or by the parenterally injected hormone substances (Fig. 5). Sochet<sup>19</sup> also reported observations of the transition of endometrial epithelium to that of tubal type

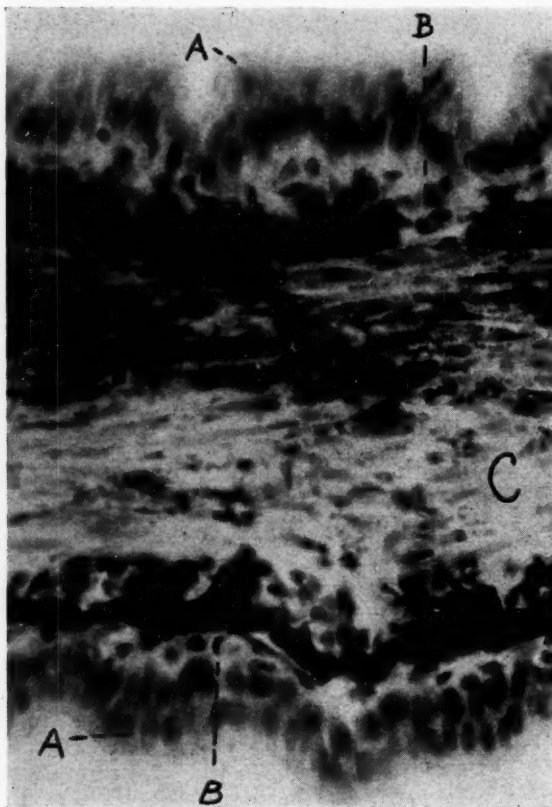


Fig. 3.—High magnification of the proliferated endometrial epithelium (A) with its stroma (B) covering both surfaces of the iris (C). This subepithelial stroma (B) is different from that of the collagenous stroma of the normal iris.

in endometrial transplants in the eyes of rabbits. Sampson<sup>11</sup> has described a similar heteroplasia at the uterotubal junction. Huber and his co-worker, Philipp,<sup>37, 38</sup> have offered convincing evidence of the frequent epithelial outgrowth, or heteroplasia, in the interstitial portion of the Fallopian tube. Te Linde and Scott<sup>12</sup> observed heteroplasia of the squamous type about the transected cervix in their experimental production of endometriosis in monkeys. We also noted a similar change in several of our animals. In both groups this change in cell type was noted only in those animals in which the anatomical location of the cervix had been surgically altered. It is a common clinical experience to encounter a similar heteroplasia in an endometrial polyp which has been extruded into the vagina through the cervical os.

Katz and Szenes<sup>20</sup> were among the first experimenters to suggest that ectopic bits of endometrium were dependent upon ovarian function. Mar-kee's<sup>11b</sup> observations also suggest that the estrous cycle and hormonal influences are very important in these explants. Traut<sup>39</sup> in 1928, by the addition of corpus luteum extract to the standard culture media, graphically demonstrated the growth-promoting influence on endometrial cells. Hobbs and Bortnick<sup>21</sup> produced endometrial lesions in the lung by injecting macerated endometrium into the blood stream. These endometrial embolic islands retained their function of undergoing decidua-like formation when stimulated with large doses of estrogenic substances. Novak,<sup>32</sup> Meyer,<sup>13</sup> and Sampson<sup>1</sup> have described and illustrated a similar decidua-like reaction in different areas in women.

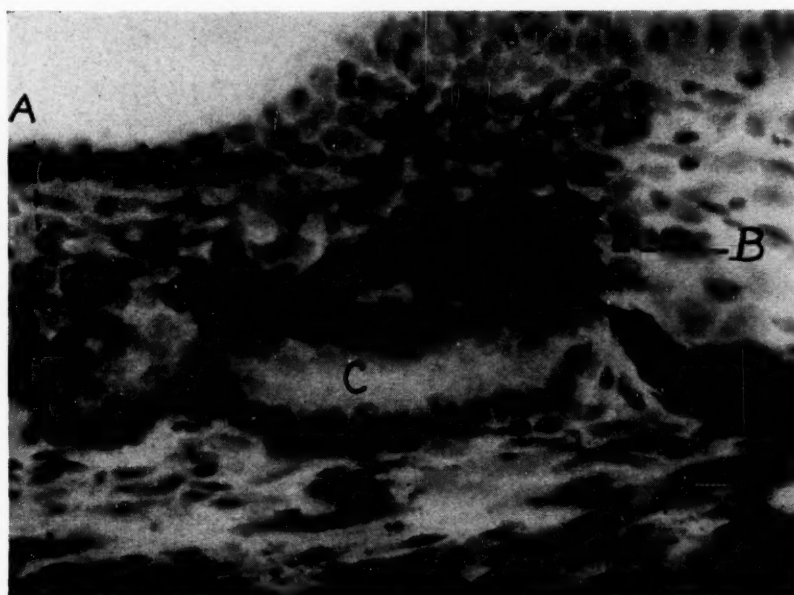


Fig. 4.—Invasion of the epithelium (A) into the substance of the iris beneath the pigmented layer (B) seems to have occurred. This proliferated epithelium has formed a simple tubular gland (C).

All evidence indicates that ovarian cells have an unusual propensity for changes in cell type and function. Almost all clinical evidence points to the fact that the ovaries are the most frequent site of heterotopic endometrial tissue. To us, the endometrial glands and stroma, separated and surrounded by the heteroplastic cells of a recent corpus luteum (Fig. 6), more strongly suggest a metaplasia rather than any form of metastatic implantation. Gruenwald<sup>24</sup> has embryologically traced the prolongations of the celomic epithelium which correspond very closely with the widespread distribution of endometrial lesions in women.

It has frequently been suggested that menstrual blood contains irritative factors. These agents when introduced into or upon foreign tissues may produce a heteroplastic change in cells which histologically and physiologi-

cally resemble normal endometrium. Te Linde and Scott,<sup>12b</sup> however, were unable to demonstrate peritoneal irritation in four monkeys who repeatedly received intraperitoneal injections of circulating blood (drawn from a leg vein) which was obtained during menstruation. This experiment suggests that if menstrual blood is important in the production of endometriosis it must be due to other formed elements in it or a substance acquired during its passage through the uterine wall or its mucosa.

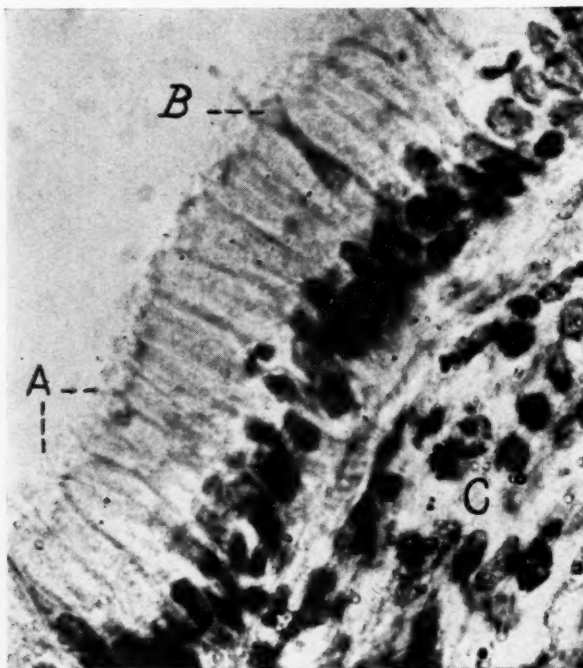


Fig. 5.—Apparent heteroplastic transformation of transplanted endometrial epithelium to that of tubal type. A, cilia, B, peg cell, C, iris.

Experiments in 1928 by Heim,<sup>23</sup> which have been widely quoted, were, in view of recent knowledge, poorly conceived and too brief in duration to prove or disprove that endometrial bits obtained from the menstruating uterus are viable. This author, working with two monkeys, opened the menstruating uterus, obtained intrauterine autologous material and scattered it throughout the peritoneal cavity or into a previously prepared peritoneal sac. In an additional animal, human menstrual blood was employed. We know today that heterologous transplants of this type of tissue will fail to survive. On inspection of the peritoneal cavities of the two monkeys thirty-nine and fifty-six days after this transplantation experiment, Heim failed in his effort to demonstrate viable ectopic endometrial tissue.

#### Tissue Culture

Many clinical reports have shown large bits of viable-appearing endometrium lying free in the various channels of transport such as the tubes, veins, and lymph spaces during and following menstruation or pelvic opera-

tive procedures. The large piece of endometrium with its stroma illustrated in Fig. 7 was found lying free in the lumen of a large vein in the lower portion of a surgically removed uterus. However, histological evidence of apparent viability is not accurate. It remains to be proved that these bits of desquamated or dislodged mucosa are capable of implantation and growth. Tissue culture, vital staining, or implantation into distant body cavities should yield additional information.



Fig. 6.—Endometrium-like glands (A), surrounded by typical stroma (B), contained in the wall of a recent normal corpus luteum cyst (C) of the ovary in the human being.

Geist<sup>28</sup> withdrew menstrual blood through a pipette one-third the diameter of the interstitial portion of the Fallopian tube. Supravital staining indicated viability of the epithelial elements up to one hour. Fischer<sup>29</sup> and Ebeling<sup>30</sup> have shown that in tissue culture the endometrial epithelium tends to grow in continuous sheets and at times assumes tubular arrangements. Carrel's<sup>31</sup> investigations suggest that the connective-tissue elements proliferate more rapidly than does the epithelium. Keettel and Stein<sup>33, 40</sup> have recently reported successful tissue culture of the castoff menstrual endometrium. Penicillin and streptomycin were added to their media to aid in bacteriostasis. Proliferation of fibroblasts and epithelioid elements occurred when the tissue culture contained estrogens and progesterone. In their absence, how-



ever, only the fibroblasts migrated from their decidual explants. Hirsch and Jones<sup>41</sup> were able on ordinary *in vitro* media to observe growth in both the stromal and epithelial elements of surgically excised human endometrium. The epithelial cells became cuboidal in type during growth periods of one month or more. Cron and Gey<sup>42</sup> concluded that castoff endometrium was viable in tissue culture, although their material was recovered from the menstruating uterus by a sharp curette. It is indeed likely, however, that viable endometrium was included in such a biopsy explant.

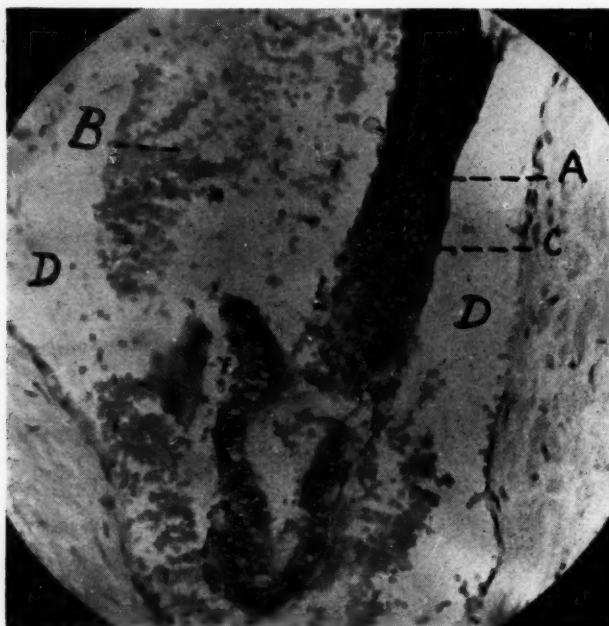


Fig. 7.—A viable-appearing piece of endometrium (A), surrounded by red blood cells (B), with stromal cells attached to it (C) lying in the lumen of a large vein (D). Found in the lower pole of a human uterine corpus removed by hysterectomy.

For many years large numbers of the higher primates have been used in the study of research problems. In addition to this, several observers, working with monkeys in their natural habitat, have reported some of the diseases which affect them and facts concerning their physiology and anatomy. Endometriosis has been rarely reported in monkeys although this may be accounted for in part on the same basis that it was overlooked or unrecognized for so long in women. We have been able to find only four reported instances of spontaneous endometriosis in the monkey. Two of these had had local pelvic or distant surgical procedures.<sup>12b, 25, 26, 27</sup>

Kluver and Bartelmez<sup>26</sup> in their beautiful description of an extensive endometriosis, which eventually caused the monkey's death, raise the question of the possible effect of disturbances in the hypothalamic region and consequent causation of "ovarian and pituitary hormonal imbalances." We have had the opportunity of seeing the microscopic preparations taken from this animal and they revealed the most extensive serosal involvement that we have

ever seen. There can be very little question from clinical observation that gynecological operations in women may be followed by marked and sometimes long-lasting change in the physiological function of the pelvic organs. Clinical reports have recorded innumerable instances of endometriosis following operations on the female genitals. These have been accepted as instances of surgical transplantation of viable endometrial tissue. We do not believe this has been adequately proved. Novak<sup>32</sup> and others have previously expressed similar doubts.

In 1950 Te Linde and Scott<sup>12</sup> contributed, we believe, another epoch-making contribution to the subject of experimental endometriosis. In these fundamental experiments on monkeys, the authors first reconfirmed the ease with which surgically excised bits of endometrium will survive after transplantation to various pelvic organs. Their remaining ten animals were surgically altered in an attempt to divert the menstrual flow into the free peritoneal cavity. During this procedure, in most instances, the lower portion of the cervix was either transected or removed. One-half of these monkeys developed endometriosis within 75 to 963 days. An additional animal, reported in their subsequent paper in 1953<sup>12b</sup> developed a very extensive endometriosis involving the bowel wall, anterior cul-de-sac, the lower portion of the uterus, kidney, and a paraureteral lymph node, which may have produced a marked hydroureter. These authors could find no evidence of heteroplasia in excised cervical tissue transplanted to distant locations in six of their animals. Transplanted tubal epithelium in six animals revealed no tendency to change in cell type and the uterotubal junctions failed to show heteroplasia similar to that described by Sampson<sup>11</sup> following salpingectomy in the human being. They also, in the Rhesus monkey, indicate by injection, histological examination, and insufflation methods, that there is no valve at the uterotubal junction. Endometriosis was found about the external cervical os outside the peritoneum in all four of their animals in which the cervix had been transplanted. This excellent article reports the fourth example of spontaneous endometriosis found in the monkey.

We wish to report the details of our work, begun Dec. 23, 1944, on the production of experimental endometriosis in the monkey. A small portion of these details have been previously reported<sup>10e, g</sup> in our discussions of the papers by Te Linde and Scott. Two series of six monkeys each (Group A and Group B) were used in these experiments. The later series (Group B) begun Nov. 26, 1948, were then divided into three pairs as controls for the methods used in the preliminary Group A. Endometriosis was found in 66 per cent of each group. In both groups the time required for the appearance of these lesions was from 472 days to 1,460 days. With the exception of one specimen removed from the serosa of a loop of bowel adherent to the posterior uterine wall (472 days), endometriosis was not found in any of the numerous biopsies taken during the long periods of observation. We believe that this was also true in Te Linde and Scott's experiments. The meaning of this observation to us is yet obscure, but we believe it is important.

In our animals in which an attempt was made surgically to divert the menstrual flow, the procedure consisted of freeing the entire cervix from its vaginal and ligamentous attachments and implanting the external os outside the peritoneum beneath the fascia of the anterior abdominal wall. Re-exploration of the peritoneal cavity was repeated at approximately six-month intervals. Biopsies of suspicious areas were done at these times. In no instance did we find free blood in the peritoneal cavity although some of these animals were operated upon at the height of discoloration of the genital skin. Several of the initial operations were done during menstruation. In a few instances a hemosiderin-like cast of the anterior cul-de-sac peritoneum was observed. Te Linde and Scott did not describe gross blood in the peritoneal cavity nor did they mention discoloration of the peritoneum in any of their animals. However, they did describe an endometrial lesion in the anterior cul-de-sac. It is interesting to speculate whether the position the monkey usually assumes would account for gravitation of blood into the anterior rather than the posterior cul-de-sac, although the majority of the described lesions from our experiments occurred in positions similar to those commonly found in women. Endometrium-like lesions found near the cervical os in our monkeys were not unequivocal and to us suggest heteroplasia of epithelium rather than implantation. Thick deposits of hemosiderin and pigment-laden phagocytes about the cervix, however, suggest blood shed into these areas. The lesions of the pelvic organs and bowel are without question endometriosis. The absence of endometriosis in those animals reported by Te Linde and Scott which developed hematocervix, hematometra, cervicointestinal fistula, or peritonitis, and tuberculosis is noteworthy. None of our animals developed known collections of blood in the genital tract. It was necessary, however, in two animals to reimplant the cervix in the abdominal wall.

We were fortunate that only one animal died during the nine years covered by this study. This death was the result of massive air embolism which followed a Rubin test. We were unable to demonstrate by x-ray the passage of Lipiodol or air in any of our monkeys in which the Rubin test was employed.

Experiments in tissue culture indicate the growth-promoting power of hormones on endometrial explants. Three animals in each group received prolonged doses of both estrogen and progesterone by parenteral, intraperitoneal, or implantation routes. One of the six animals developed an external endometrium-like lesion on the uterine fundus (Fig. 16). Two additional animals developed endometriosis, but they were subjected also to cervical implantations.

Abbreviated protocols of individual animals follow and are summarized.

### Group A

MONKEY 1.—Dec. 23, 1944. Two-month study.

Laparotomy during menstrual period. Attempted Rubin test unsuccessful; hysterotomy; endometrial bits scattered in posterior cul-de-sac; 62 days later cervix freed; repeat Rubin test unsuccessful. Animal died of extensive air embolism. No evidence of endometriosis.

MONKEY 2.—March 17, 1945. Forty-eight month study.

Cervix implanted *through* abdominal wall; 5 Rubin tests followed by two Lipiodol,

negative to x-ray; 16 months later laparotomy, no evidence of endometriosis; 12 months later cervix freed, amputated, and buried beneath rectus fascia; spontaneous cervico-abdominal fistula; 5 months later reburied. Biopsies from cervical area did not reveal endometriosis. Six months cervix reburied; one month later cervix opened spontaneously, cauterized; 3 months later panhysterectomy.

**Pathology** (Figs. 8, 9, 10, 11, 12): Endometrioma of right ovary, adenomyosis, endometrial implants on sigmoid colon, large adenomyoma of rectovaginal septum (?).

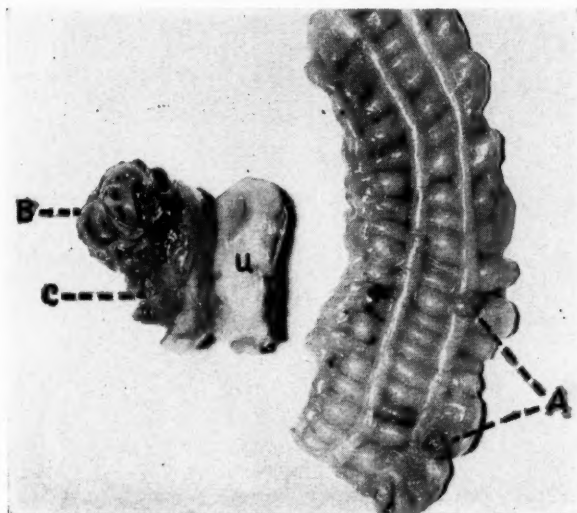


Fig. 8.—Endometriosis of the sigmoid colon (A), ovary (B), rectovaginal septum (C), adenomyosis (u). (Monkey 2.)

**MONKEY 3.**—Sept. 26, 1945. Twenty-eight month study.

Cervix freed and allowed to drop into abdominal cavity. Seven months later no evidence of endometriosis or gross blood; 10 months later similar findings, cervix buried beneath rectus fascia; 11 months later panhysterectomy.

**Pathology** (Fig. 13): Marked adenomyosis, menstruating adenoma of mesosalpinx.

**MONKEY 4.**—Dec. 26, 1945. Thirty month study.

Laparotomy Dec. 26, 1945. During next 10 months 515 mg. progesterone in sesame oil injected into peritoneal cavity in 5 mg. doses; menstruation recorded three times during this interval: Sept. 24, Oct. 14, and Nov. 25, 1946; twelve months later, laparotomy; no reaction to injected material; no endometriosis. Cervix bisected and implanted into anterior abdominal wall; cervix retracted and remained buried in anterior abdominal wall. For next 6 months (Dec. 12, 1946 to May 29, 1947) 600 mg. progesterone in sesame oil injected into peritoneal cavity in 5 mg. doses. Twelve months later laparotomy; cervix completely occluded. Fifty milligrams crystalline progesterone implanted in right thigh and repeated Jan. 8, March 24, and April 27, 1948. A total of 1,315 mg. progesterone given over period of 41 months. Laparotomy May 18, 1948; marked adhesions. Panhysterectomy.

**Pathology:** Marked (menstruating?) adenomyosis.

**MONKEY 5.**—Jan. 30, 1946. Eighteen month study.

Laparotomy; 110 c.c. sesame oil intraperitoneally, 1 c.c. doses for 11 months; Laparotomy; Multiple peritoneal biopsies negative for endometriosis; Cervix implanted; 110 c.c. more sesame oil intraperitoneally for six months; panhysterectomy.

**Pathology:** Endometriosis, left mesosalpinx.





Fig. 9.—Endometrioma of the sigmoid colon (A), sagittal section. Bowel mucosa (B). (Monkey 2.)

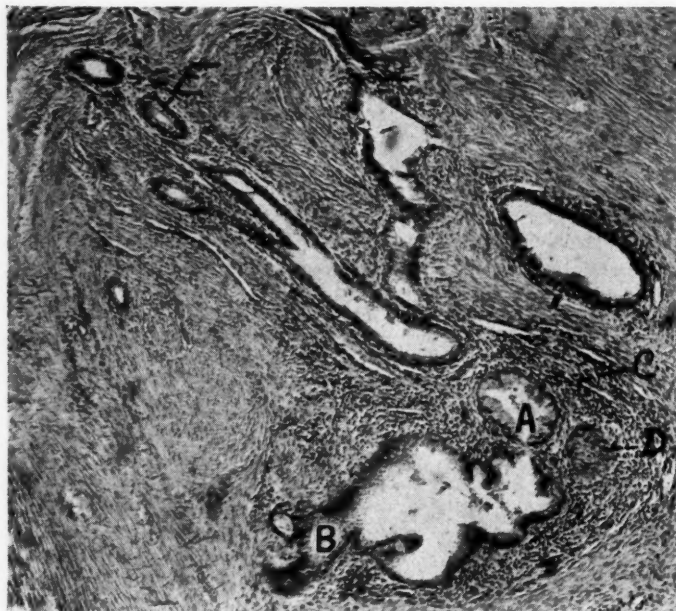


Fig. 10.—Monkey 2. Adenoma rectovaginal septum. Apparent transition of typical cervical epithelium (A) to endometrium-like cells (B). Surrounding stroma (C) contains also a nest (D) of squamous-appearing cells. More characteristic endometrial glands (E).

**MONKEY 6.**—Feb. 27, 1946. Twenty-three month study.

Laparotomy; estradiol in 0.2 mg. doses given until Nov. 29, 1946. Cervix implanted under abdominal fascia; panhysterectomy Jan. 1, 1948.

*Pathology:* No endometriosis found.

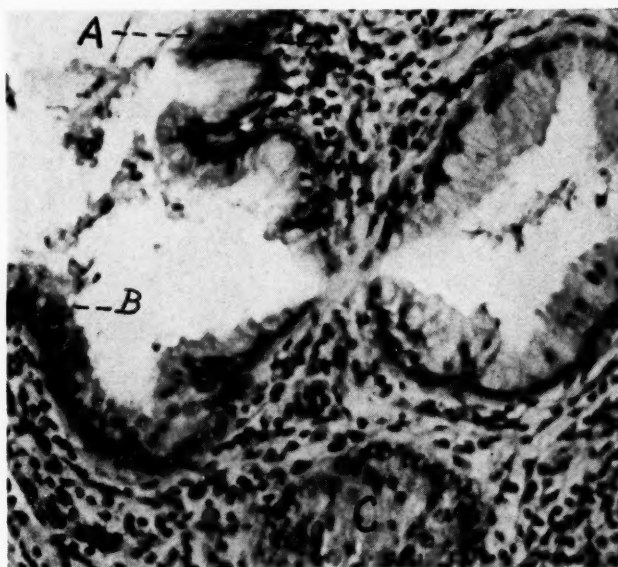


Fig. 11.—High-power magnification of Fig. 10, showing details of the stroma (A) and the apparent epithelial heteroplasia (B). Nest of squamous cells (C). (Monkey 2.)

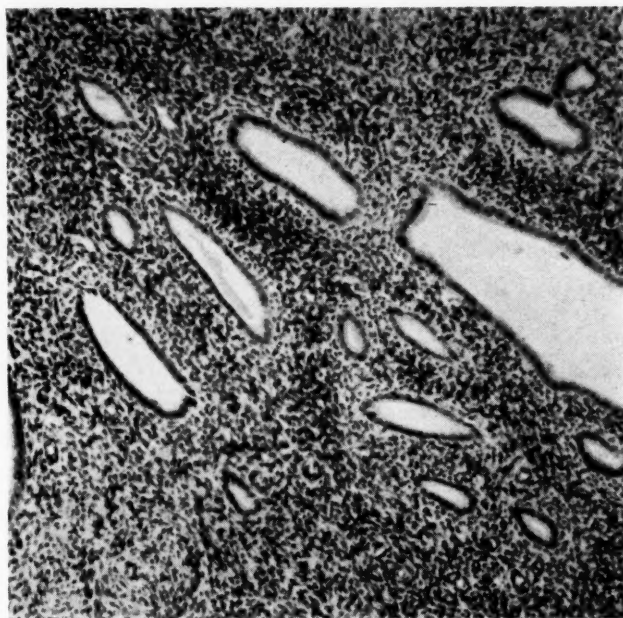


Fig. 12.—Adenomyosis. (Monkey 2.)

**MONKEY 7.**—Aug. 12, 1946. Twenty-one month study.

Laparotomy. From Aug. 22, 1946, to May 21, 1947, 1,300 mg. of progesterone and 58 mg. estradiol injected almost daily intraperitoneally in doses of 5 mg. progesterone and

0.2 estradiol. Laparotomy on Jan. 22 and May 23, 1947; no gross or microscopic evidence of endometriosis; 150 mg. crystalline progesterone implanted in left thigh in 3 divided doses; twelve months later panhysterectomy; no evidence of endometriosis.



Fig. 13.—Monkey 3. Endometriosis of mesosalpinx (A), bloody extravasation (menstruating?) in stroma (B), tubal lumen (C).

### Group B

MONKEY 8.—Nov. 26, 1948. Forty-four month study.

Laparotomy during menses; no peritoneal blood; cervix implanted; laparotomy in 9 months negative for endometriosis; 7 months later laparotomy again negative; 5 months later again negative. Panhysterectomy 23 months later.

*Pathology:* Scattered adenomyosis, adenoma, level of internal os.

MONKEY 9.—Nov. 28, 1948. Forty-six month study.

Laparotomy, cervix implanted; ten months later cervix free in pelvic cavity; os occluded; no free blood; marked adhesions. Six months later cervix reimplanted (Fig. 14). Biopsy; adherent rectosigmoid (endometrioma); six months later, laparotomy negative. Two years later panhysterectomy.

*Pathology* (Figs. 15 and 16): Endometrioma of sigmoid, endometriosis (?) or heteroplasia (?) of cervical lip.

MONKEY 10.—Dec. 15, 1948. Forty-five month study.

Laparotomy; cervix implanted; ten months later marked omental and bowel adhesions; biopsies negative; 5 months later biopsies repeated; 8 months later, again repeated; 22 months later, panhysterectomy.

*Pathology:* Adenomyosis (menstruating?), endometriosis (?), heteroplasia (?) of cervical lip.

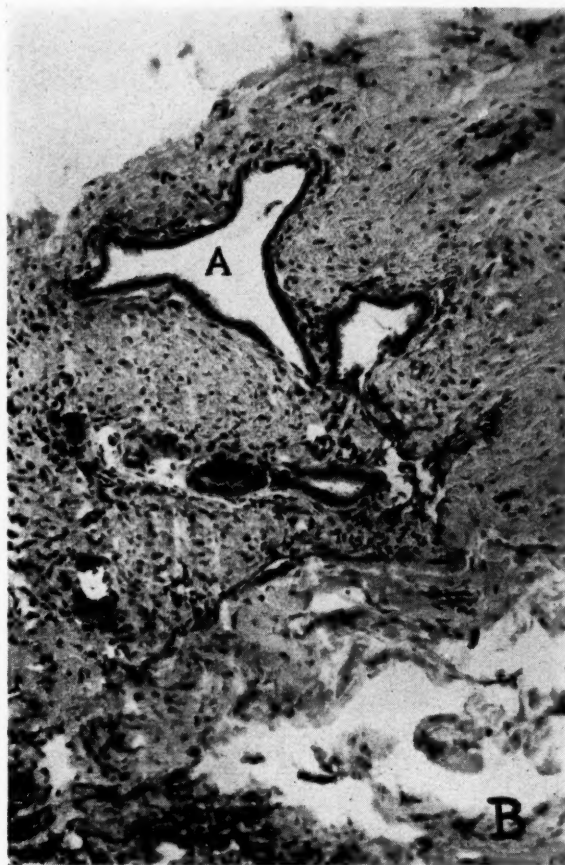


Fig. 14.—Monkey 9. Endometrial implant (A), sigmoid wall (B). Biopsy specimen after 472 days of study.

MONKEY 11.—Jan. 18, 1949. Forty-three month study.

Laparotomy; pelvic organs not disturbed; 590 mg. intraperitoneal progesterone during study (5.0 mg. doses); four additional laparotomies for observation; panhysterectomy Aug. 19, 1952.

*Pathology* (Fig. 17): Endometrioma (?) or infolding (?) peritoneum, overlying fibrinous adhesion.

MONKEY 12.—Jan. 18, 1949. Forty-five month study.

Laparotomy negative; pelvic organs not disturbed; 515 mg. intraperitoneal progesterone during study (5.0 mg. doses); at third laparotomy, animal found pregnant; male delivered May, 1951. Panhysterectomy Oct. 27, 1952.

*Pathology:* None found.

MONKEY 13.—February 8, 1949. Forty-five month study.

Laparotomy negative; pelvic organs not disturbed; 515 mg. intraperitoneal progesterone (5 mg. doses); three inspection laparotomies; panhysterectomy Nov. 3, 1952.

*Pathology:* No endometriosis, benign endocervical polyp.



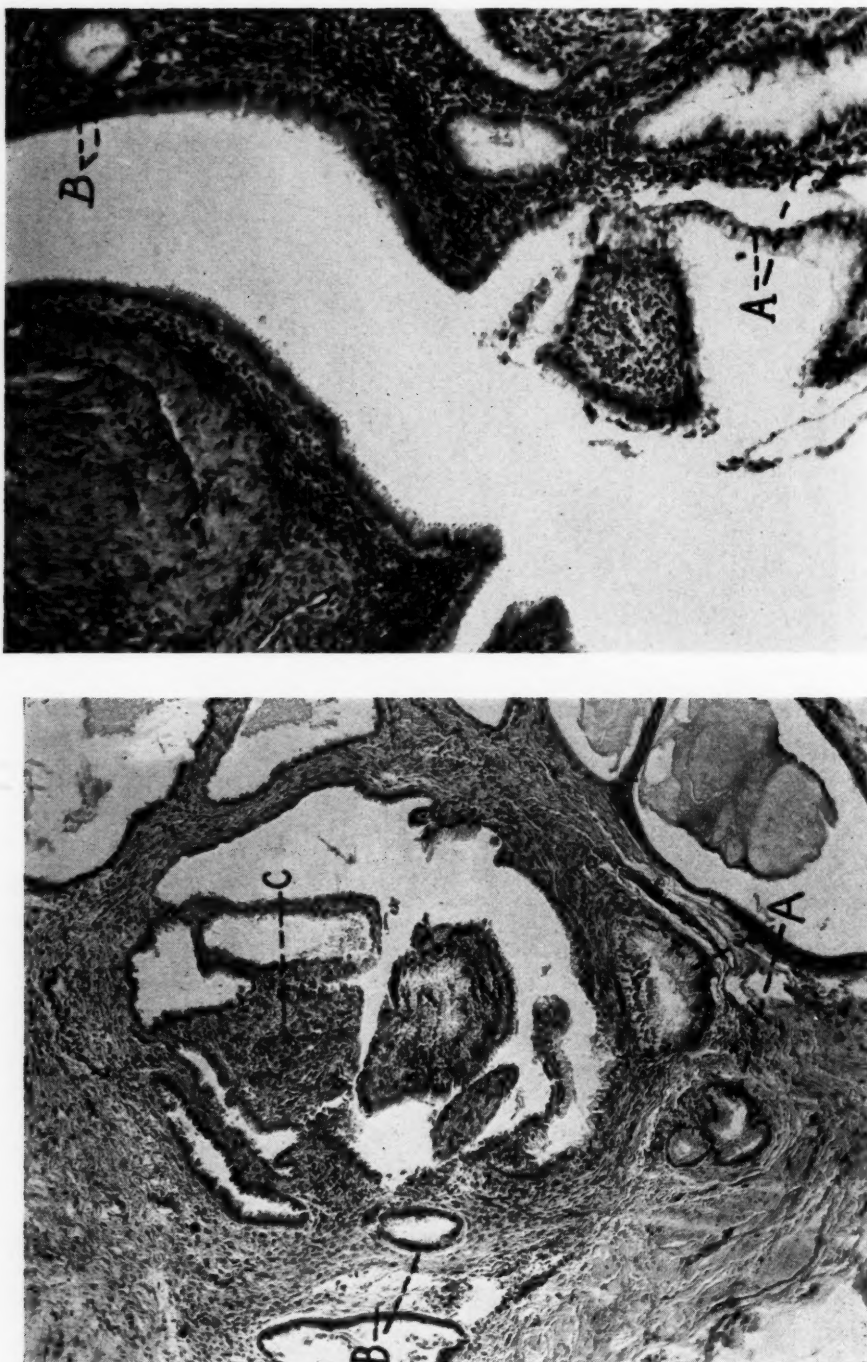


Fig. 16.

Fig. 15.

Fig. 15.—Details of cervical architecture from an implanted cervix taken from a monkey in Group B. This clearly demonstrates the difficulties of microscopic interpretation of differences in cell type in this region. Cervical (A), endometrium-like (B), and squamous-like (C). (Monkey 9.)

Fig. 16.—Higher magnification of a similarly implanted cervix taken from an animal in Group B. Note typical cervical epithelium (A), as compared to endometrium-like cells (B). (Monkey 9.)

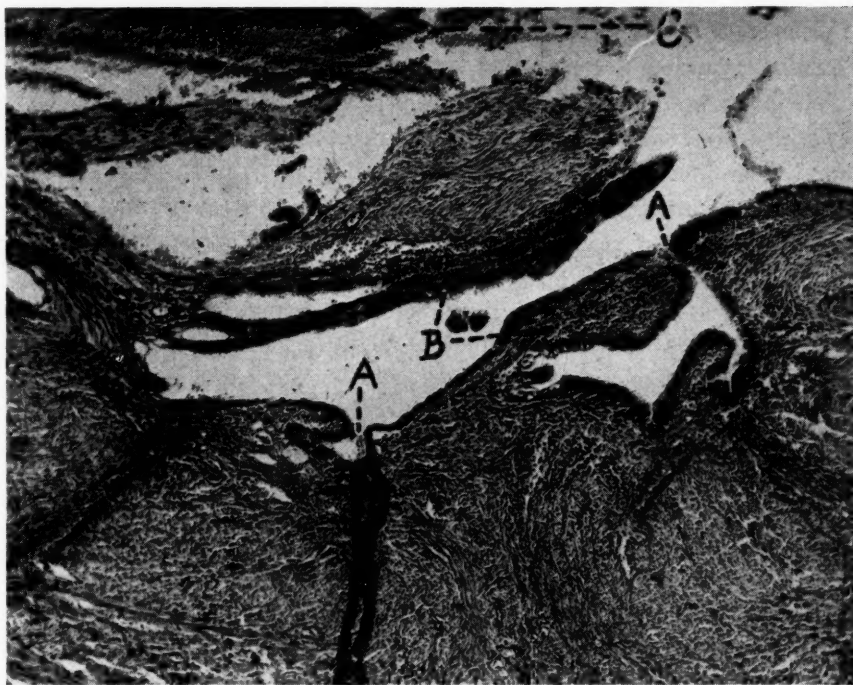


Fig. 17.—Transition and/or invasion of serosal epithelium of the uterine fundus (A), stromal development quite marked (B). Adherent overlying fibrinous exudate (C), so characteristic of external endometriosis. (Monkey 11.)

### Conclusions

1. Endometriosis resembling that found in women may be readily produced in the Rhesus monkey by several different surgical procedures.
2. Endometriosis has not, to our knowledge, been experimentally produced in the monkey by other methods than surgical ones.
3. Endometriosis in women following surgical procedures has been accepted as caused by mechanical transplantation of viable endometrial tissue. This thesis still remains to be proved.
4. Until positive proof to the contrary is forthcoming, experimental surgically produced endometriosis in the menstruating animal should be based on the same premise.
5. Repeated transperitoneal surgical procedures preceded the occurrence of all endometriosis in our series of monkeys as well as in those of Te Linde and Scott.
6. Endometriosis seems to occur rather suddenly after varying but usually long intervals of time and following varied surgical procedures involving the genital organs.
7. With one exception (Monkey 11), when simple laparotomies were performed for inspection only, and no surgical manipulations of the genital organs were done, endometriosis failed to occur.

8. Prolonged parenteral, intraperitoneal, or intramuscular implantation of estrin, progesterone (or their vehicles) did not seem to influence the appearance of endometriosis unless accompanied by surgical alterations in the pelvic organs.

9. We have not, nor do we believe other investigators have observed, in the experimental animal, regurgitation or discharge of menstrual blood or desquamated endometrium into the free peritoneal cavity.

10. Te Linde and Scott have furnished proof from four animals that circulating blood from a leg vein obtained during the menstrual period and injected into the peritoneal cavity did not produce endometriosis.

11. Therefore, if menstrual discharge does cause endometriosis, the substance or substances responsible must be acquired in its passage through the uterine wall or its mucosa.

12. Until this discharge can be obtained by other than surgical means and transferred to distant body cavities, thus producing endometriosis, its etiology is still obscure. The menstruating monkey is an ideal animal for this experimental problem.

13. Extraperitoneal lesions about the transplanted external os, in our animals, were not unequivocal for endometriosis and we believe suggest heteroplasia rather than transplantation.

14. True endometrium-like lesions produced experimentally in the monkey correspond geographically to those usually found in the human being. This distribution is limited to those primary embryonic cells from which the genitals originally develop.

15. The character and distribution of the fine peritoneal fibrinlike adhesions which so regularly accompany endometriosis in the monkey and the human being suggest the presence of an irritative factor.

16. The contiguity of this adhesive tissue with the infolding of the serosal covering of the corpus uteri to form a typical endometrium-like island of tissue (Fig. 17) suggests a similar irritative etiology.

17. The apparent etiological element of time required to produce these experimental lesions may be less important than the increased number of surgical procedures utilized.

We wish to thank Ciba Pharmaceutical Products, Inc., for supplying all experimental hormones for this study.

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**BENIGN TROPHOBLASTIC LESIONS IN MATHIEU  
CHORIONEPITHELIOMA REGISTRY (HYDATIDIFORM MOLE,  
SYNCYTIAL ENDOMETRITIS)\***

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**W**E<sup>9</sup> HAVE recently published a study of the 74 cases of choriocarcinoma which had been encountered in the material of the Mathieu Memorial Chorionepithelioma Registry of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons up to Sept. 1, 1953. This, we believe, represents the largest number of authenticated cases available for direct study by any one group of investigators, and conclusions based on such a material would seem far more reliable than those yielded by collective studies based on cases reported in the literature, but often of doubtful authenticity.

A very valuable by-product of the Chorionepithelioma Committee's primary purpose of collecting and studying malignant choriocarcinomas has been the accumulation of a large group of benign trophoblastic lesions. The committee, in the early announcement of its purposes, deliberately appealed to gynecologists, obstetricians, and pathologists to send to the Registry all types of pregnancy material in any way cognate with choriocarcinoma, and this obviously included hydatidiform moles of various types, as well as such benign trophoblastic lesions as the so-called syncytial endometritis. The purpose of this appeal was not merely the academic one of accumulating such material for comparative studies, but also because of the long-recognized fact that lesions of this benign trophoblastic group are so often incorrectly diagnosed as choriocarcinoma.

The correctness of this suspicion has been amply confirmed by the experience of our committee, as reported in our previous paper. During the same period of our work which yielded 74 cases of genuine choriocarcinoma, there were no less than 85 cases sent in to us with the diagnosis of choriocarcinoma, but which our own study, together with follow-up studies, convinced us to be nonmalignant. We ought here to emphasize that the present paper must be looked upon as a supplement to our previous one on choriocarcinoma, since there is some overlapping of their contents because of the frequent necessity of contrasting the benign with the malignant lesions. Since we are anxious to avoid repetitiousness in either verbal or photomicrographic descriptions, the reader must be referred to the previous publication for further elaboration.

\*Published under the sponsorship of the Mathieu Chorionepithelioma Committee of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. This committee consists of Drs. John I. Brewer, Willard A. Cooke, R. A. Ross, and Emil Novak, Chairman. Dr. Seah's participation in this study was made possible by a Fellowship of the World Health Organization.

Malignancy as it occurs in trophoblastic lesions is determined by the microscope, as it is in all fields of pathology, and not by the clinical course. For example, if a trophoblastic neoplasm is microscopically an unquestionable choriocarcinoma, but the patient gets well, the honest conclusion is that some patients with this disease survive, and the incorrect one would be the cynical statement sometimes heard that the patient could not have had a choriocarcinoma just because she got well. One might just as well deny the malignancy of innumerable invasive cervical cancers just because they were cured by treatment.

We were greatly interested in the group of 85 cases which had been wrongly diagnosed as choriocarcinoma, and hence we have thought it would be of special interest to review this group of nonmalignant lesions, in an effort to determine, if possible, the reasons for the incorrect diagnoses of malignancy which had been made in them.

The microscopic characteristics of choriocarcinoma are now so well established that false negative diagnoses should be rare, i.e., a genuinely malignant tumor will not often be called a benign lesion. The mistakes are almost always in the other direction, a benign lesion being incorrectly diagnosed as choriocarcinoma. It should, therefore, be of value to try to explain the great incidence of the false positives which have done so much to vitiate the literature of the subject, and hence this review of our benign lesions, including the 85 cases in which a false positive diagnosis of malignancy had actually been made.

### Material

Up to Sept. 1, 1953, 154 cases of hydatidiform mole and 27 cases of syncytial endometritis were contributed to the Registry. The mole group included 120 which were classified as frankly benign and 34 which we put under the intermediate designation of chorioadenoma destruens. Parenthetically, it is hardly necessary to say that the occurrence of only 154 cases of mole in the same general Registry material which yielded 74 cases of choriocarcinoma of course throws no light on the relative incidence of the benign and malignant groups, since the Registry material is so heavily weighted by its primary interest in the malignant group.

All of the 85 false positive diagnoses were made in the three lesions above enumerated except 7 (See Table VII). Of these 7, there were 5 of simple abortion, 1 of normal decidua with a very early ovum implantation, and 1 case of degenerated tissue showing no trophoblastic tissue at all. All these 7 mistaken diagnoses were of obvious crass type, and they call for no discussion, while the remaining 78 do throw light on some of the more common pitfalls of diagnosis.

As in our recent study of the choriocarcinomas in the Registry material, our purpose has been an analysis and factual study of our own material rather than a dissertation on the general subject or a review of the literature. Moreover, as with the choriocarcinomas, we feel that the character and limitations of the Registry material make it of somewhat less value in the consideration of hormonology and associated ovarian changes than in the study of the pathology, pathologic differentiation, prognosis, and treatment of the benign trophoblastic lesions.

**Benign Hydatidiform Mole**

Though there are differences in the estimates of the incidence of hydatidiform mole, the figure usually quoted is 1:2,500 pregnancies. It appears to be accepted, also, that both the benign mole and choriocarcinoma are disproportionately more common in certain geographic areas of the Orient, especially China, the Philippines, and Malaya. As a matter of fact, it has been estimated (Seah) that the incidence of hydatidiform mole in these sections is about 1:200 to 300. No adequate explanation has been advanced for this, though some have suggested that the higher incidence is linked up with the higher degree of parity in the women of these Oriental areas. This hypothesis, it will be seen, is not supported by our Table II.

TABLE I. AGE INCIDENCE OF HYDATIDIFORM MOLE

Below 20 years	20
20-30	71
31-40	19
41-50	7
Over 50	2
Age not known	1
Total	120

TABLE II. PARITY

Para 0	38
1	27
2	24
3	4
4	4
5	5
6	3
7	3
8	1
9	1
Parity unknown	10
Total	120

As a matter of fact, one is impressed by the low degree of parity or the nulliparity in such a large proportion of our cases, 89 of our 120 patients having had no more than 2 pregnancies, and 38 being nulliparas. No such preponderance of low parity was seen in our choriocarcinoma cases, and the difference does not seem explainable by any differences in age incidence of the two groups. For example, the bulk of the malignant group, 59 out of 74, occurred between the ages of 20 and 40, while 97 of the 120 benign moles were noted in women of the same age group.

*Clinical Symptoms.*—Since these are well known, they need not be here reviewed except to say that the chief initial symptom is usually the bleeding which manifests itself, most often at the third or fourth month of pregnancy. While the first suspicion is likely to be of threatened miscarriage, this may be thrown into doubt by the disproportionately large size of the uterus for the stage of gestation. The inability to palpate the fetal parts even when the uterus is enlarged to the umbilicus or beyond, the absence of fetal heart signs,

the negative x-ray findings, the spontaneous expulsion of the characteristic vesicles, all these help to focus on the probability or certainty of hydatidiform mole.

*Hormone Tests in Hydatidiform Mole.*—The biologic methods of study which have been employed for the past quarter of a century are often of great help, though they are not as diagnostically valuable as was once hoped. When their limitations are recognized, however, they are often very useful. It is obvious that a single gonadotrophic titer can have no diagnostic value in the early stages of pregnancy, when the normal titer is very high, sometimes higher than with a mole. If, however, the titer remains high or increases beyond the third month of pregnancy, its diagnostic value is far greater, though it still is not in any way helpful in the differentiation of benign and malignant lesions.

Of our 120 cases of hydatidiform mole only 35 had any worth-while hormonal follow-up.

In 18 of the 35 cases, the pregnancy test became negative within two months of the evacuation of the mole. Of the 17 cases in which the test was still positive two months after evacuation of the mole, hysterectomy was done in 6 cases (C.R. 7, 42, 138, 142, 169, 203). In these, microscopic examination showed residual but benign tissue in the uterus. In all these cases a negative pregnancy test was noted postoperatively.

In another 3 cases (C.R. 38, 43, 224) the test became negative only after repeat dilatation and curettage removed some residual molar tissue. In another two cases (C.R. 1, 110) no residual molar tissue was found, but the removal of enlarged cystic ovaries resulted in an almost immediately negative pregnancy test. In another case (C.R. 22) the removal of residual molar tissue in the uterus, as well as enlarged cystic ovaries at laparotomy resulted in a negative pregnancy test. In C.R. 154, the pregnancy test remained positive for more than 3 months after subtotal hysterectomy for a benign mole. Interestingly enough, later examination of the cervix showed it to contain a trophoblastic node. After trachelectomy the test became negative.

In C.R. 113 the tests remained positive until the death of the patient thirteen months after hysterectomy. As was stated in a previous section, the death of the patient was said to be due to trophoblastic metastases in the lungs and spine although no autopsy was performed.

In C.R. 194 the pregnancy tests remained positive from the time of evacuation of the mole until nine months later when choriocarcinoma was diagnosed at curettage. But in this nine months' period there was a six months' period of amenorrhea, which brings up the strong possibility of another pregnancy. This case serves to illustrate how important it is for a patient who has had a molar pregnancy to avoid another pregnancy for at least another year so as not to confuse the hormone follow-up.

In the remaining two cases (C.R. 65 and 111) the pregnancy tests did not become negative until two and one-half months after evacuation of the mole. We could find no reason why the tests remained positive this long.

It may therefore be said that in the majority of cases the pregnancy test should become negative within two months after evacuation of the mole. If it is still positive after this period of time the possibilities are:

1. There is residual benign trophoblastic tissue in the uterus.



2. Enlarged cystic ovaries, which apparently may serve as a reservoir for the hormones, may be present.
3. Choriocarcinoma or chorioadenoma destruens may have developed.
4. The patient may be pregnant again.

The most common of these possibilities is, of course, the first, but because choriocarcinoma is such a lethal disease, if the possibility of another pregnancy can be ruled out, one would be justified in doing a hysterectomy, especially when a repeat curettage fails to produce a negative test.

*Microscopic Appearance.*—The main pathologic changes which characterize hydatidiform mole are:

1. Trophoblastic proliferation.
2. Edema of stromal cells.
3. Absence or extreme scantiness of blood vessels.

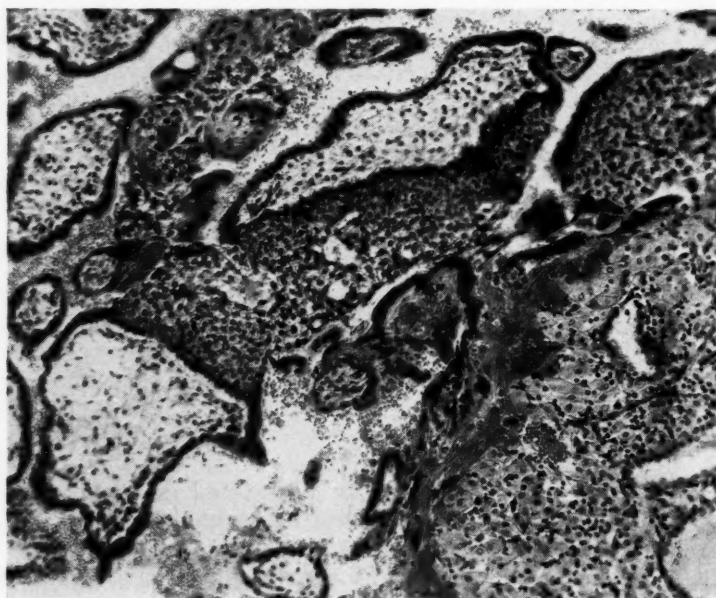


Fig. 1.—Normal uteroplacental junction of a 12 weeks' pregnancy, showing a considerable degree of trophoblastic proliferation. (Kindness of Dr. George W. Anderson, Department of Obstetrics, Johns Hopkins Hospital.)

It is well to recall that if one compares young normal placental tissue (ten to twelve weeks' pregnancy) with full-term placental tissues, the following points are at once apparent. The young villi are larger than the mature villi and their stromal cells are much scantier. The blood vessels in young villi are also much smaller than those in the older villi. Not only do the young villi have a fairly complete covering of Langhans' cells and syncytium, in comparison to the syncytial layer alone left in the older villi, but there is also a moderate degree of trophoblastic proliferation, especially at the placental-uterine junction, as shown in Fig. 1. It appears, therefore, that there is an abnormal persistence

of these immature characteristics in cases of hydatidiform mole, tending to support the theory advanced by Hertig and Edmonds<sup>3</sup> that such moles are a type of "missed abortion." We mention this similarity between hydatidiform mole and immature but otherwise normal trophoblastic tissue, because we be-

Fig. 2.

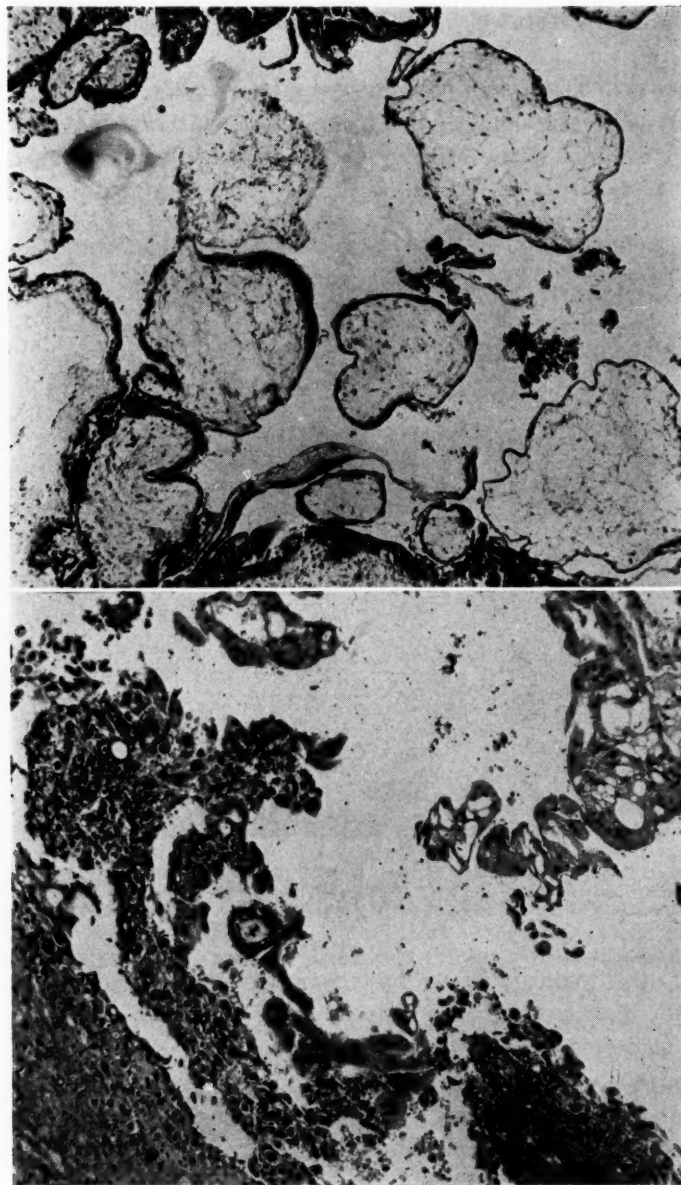


Fig. 3.

Fig. 2.—Extruded molar tissue (C.R. 57) with practically no trophoblastic covering. Compare with Fig. 3.

Fig. 3.—Portion of same benign mole seen in Fig. 2 near to its attachment in the uterus, showing marked trophoblastic overgrowth. Other examples of these contrasts are illustrated in our previous paper.

lieve that in the past mistakes have often been made in confusing one with the other, especially by those authors who have reported a high incidence of hydatidiform mole formation in ectopic pregnancies.

Of all the changes that characterize hydatidiform mole the trophoblastic proliferation is the most interesting and most important. This change varies in different parts of the mole, being greater where it is nearest the uterine wall or still implanted within it, and less when the mole grows away from the uterine wall and its source of blood supply (Figs. 2 and 3). When the trophoblastic overgrowth is unduly exuberant the lesion may be designated a chorioadenoma destruens, although this criterion of the latter lesion is not as reliable as that of perforation of the uterine wall or infiltration of parametrium and/or vagina.

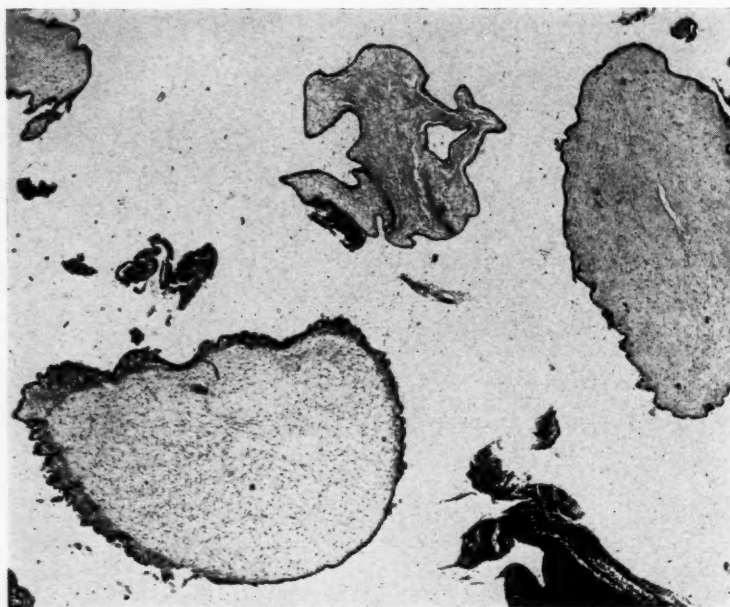


Fig. 4.—Histologically entirely benign mole (C.R. 240) from extruded tissue, August, 1951. Persistent bleeding and positive hormone tests, in spite of repeated dilatation and curettage, hysterectomy July 7, 1952, death September 12, 1952, with extensive metastasis of choriocarcinoma.

We are frank to say that we have found no feature of the gross or microscopic picture of extruded or curetted molar tissue to be of much value as indicating whether a particular hydatidiform mole will pursue a benign or malignant course. Hertig and Sheldon,<sup>4</sup> and lately Hunt, Randall, and Dockerty have tried to correlate the degree of trophoblastic proliferation, anaplastic changes, and stromal invasion of trophoblast with the subsequent course of the disease. From our study of these 120 cases of hydatidiform mole and the molar tissue submitted with our 26 cases of choriocarcinoma which have followed hydatidiform moles, we have been unable to support this proposition. The molar tissue in many cases which have eventually developed choriocarcinoma shows only very slight trophoblastic proliferation, while many of our cases of

hydatidiform mole show marked trophoblastic proliferation, although they have pursued a benign course after only a dilatation and curettage (Figs. 4 and 5).

As we have stated in our previous paper the question of anaplasia in trophoblastic tissue is a very difficult one. We have found, as have Wislocki and Bennet and various other writers, that young cytotrophoblastic cells tend to show great variations in cell size and shape, nuclear size, shape, and staining. Then, too, the degenerative processes of pyknosis and karyorrhexis are often confused with cell anaplasia.

As was shown in our previous paper, only 39.2 per cent of cases of choriocarcinoma resulted from hydatidiform mole. This is lower than the usual figure of 50 per cent and we believe it is so, because in the past cases of highly proliferative benign moles may have been classified as choriocarcinoma, a mistake which we hope we have avoided.

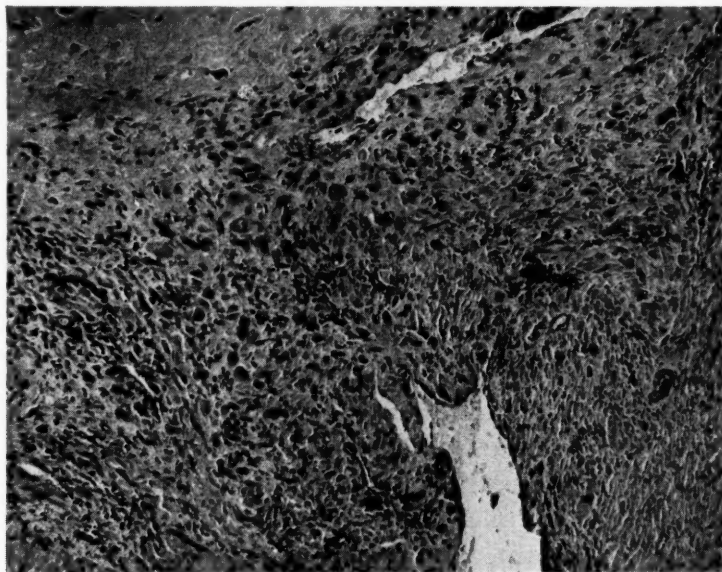


Fig. 5.—Myometrial infiltration by trophoblastic cells, which may be seen with normal pregnancy or benign mole, led to incorrect diagnosis of choriocarcinoma in this case (C.R. 22). Other instances of syncytial endometritis illustrated in previous paper.

*Treatment.*—As can be seen in Table III, 99 moles were evacuated vaginally, 11 were evacuated by abdominal hysterotomy, in 8 cases hysterectomy was performed with the mole in situ, and in one case a cesarean section was performed on a mistaken diagnosis of placenta previa. Of the 99 cases which were evacuated vaginally, 36 patients eventually had hysterectomies and of the 11 evacuated by abdominal hysterotomy, 5 eventually had hysterectomies done. All in all, 49 patients had their uteri removed. A more detailed account of the treatment given is shown in Tables IV and V. We must again remind the reader that the preceding figures represent a factual report of the procedures actually carried out in these hydatidiform moles sent to the Registry, by many different individuals and clinics in all parts of the country, and do not always represent ideal methods of therapy.



TABLE III. METHODS ADOPTED TO EVACUATE THE MOLE

Per vaginam	99
Abdominal hysterectomy	11
Hysterectomy with mole in situ	8
Cesarean section	1
Died before evacuation	1
Total	120

TABLE IV. SURGERY FOLLOWING VAGINAL EVACUATION OF MOLE

Spontaneous evacuation, no surgery	1
Spontaneous evacuation followed by hysterectomy	5
Had 1 curettage	36
Had 2 curettages	24
Had 3 curettages	2
Had 1 curettage followed by hysterectomy	17
Had 2 curettages followed by hysterectomy	12
Had 3 curettages followed by hysterectomy	2
Total	99

TABLE V. SURGERY FOLLOWING ABDOMINAL HYSTEROTOMY

No further surgery	5
Hysterotomy followed by 1 curettage	1
Hysterotomy followed by hysterectomy	2
Hysterotomy followed by 1 curettage and hysterectomy	3
Total	11

The general plan of management of hydatidiform mole which seems safest and most rational to us is as follows: Evacuate the mole vaginally with ovum or sponge forceps and follow this, preferably four or five days later, by a careful curettage of the uterine cavity. It is probably better to wait these few days before curettage to permit the uterus to contract and thus lessen the danger of perforation. If, after this, there is no recurrence of hemorrhage, the uterus involutes normally, and the pregnancy test becomes negative within two months, the danger of a malignant change may be considered over, though it would probably be safer to have a pregnancy test done and a physical checkup monthly for another six months. If, however, the bleeding should persist after the curettage, and the uterus fail to involute properly, especially in the presence of a persistent or rising gonadotrophic titer a second dilatation and curettage is advisable. Following this, if the symptoms should persist or the curettings appear highly suspicious of choriocarcinoma with broad fields of trophoblast and no villi, a hysterectomy is justified, but, in most instances, all that will be found in the uterus when it is removed will be some residual benign molar tissue deep in the uterine wall beyond the reach of the curette. Occasionally, however, a true choriocarcinoma will be found, and the hysterectomy seems justified by the gravity of the prognosis in choriocarcinoma. The second curettage appears advisable because of the uncertainty of completely removing all molar tissue at the first curettage. We believe the short period of time lost by this procedure is made worth while when one considers the number of uteri it may save.

If the patient is over 35 years old, and further pregnancies are not important, and the mole is large, total hysterectomy with the mole in situ may be considered. This is done not so much to save the patient and the doctor from a rather tedious follow-up but to avoid the rather massive hemorrhage which vaginal evacuation of a large mole may entail. The actual operation should not be any harder than a total hysterectomy for a rather large myoma.

*Metastases.*—In a discussion of trophoblastic lesions, it may be well to recall that normal trophoblast exhibits some of the attributes which we normally associate with malignancy. The ovum is implanted in the endometrium by a process of destructive invasion and there is often a physiologic metastasis of trophoblast to the lungs, this being even at times associated with slight attacks of hemoptysis, even though no lesion may be demonstrated on x-ray examination. However, probably as a result of the still unknown local and systemic defensive mechanism the trophoblastic invasion of the uterine wall is held in normal restraint, and the trophoblast in the lungs apparently undergoes spontaneous lysis.

In our series 6 cases (C.R. 31, 42, 65, 113, 154, and 259) showed pulmonary nodular densities which were interpreted by radiologists as probably metastatic growths.

Case C.R. 42 was also suffering from chronic nephritis with hypertension and died 18 months later of cerebral hemorrhage. At postmortem examination, however, no evidence of trophoblastic metastasis was found in the brain, lung, or other organs and the cause of death was attributed to chronic nephritis.

In Case C.R. 113 the patient showed clinical signs of a spinal tumor two weeks after a hysterectomy in which the uterus showed only residual molar tissue. She died thirteen months later. No autopsy was performed, but death was said to be due to metastases in the lungs and spine. Since the urinary Friedman test had remained positive right up to the time of the patient's death, the evidence is very much in favor of the metastases being trophoblastic in nature.

In Case C.R. 154 there was x-ray evidence of metastases in the lungs and femur after hysterectomy. This case was treated by hysterectomy with the mole in situ, and the only section sent to us was that of the uterine contents. This showed only a perfectly benign mole, though it is quite possible that choriocarcinoma may have been present in other parts of the uterus. This is very improbable since the patient is still alive four years after the hysterectomy.

In Case C.R. 31 x-ray examination showed a density in the right lower lobe. The patient was given deep x-ray chest therapy. The lesion resolved, and the patient has stayed well. X-ray showed metastatic nodules in both lungs in Case C.R. 65. The lesions, however, regressed spontaneously, and the patient has stayed well. A similar picture was seen in Case C.R. 259, but since this case has been sent in to the Registry only recently, we have no follow-up on her.

These cases serve to illustrate that while x-ray evidence of metastases in cases of choriocarcinoma is rightly considered a matter of grave import, the same finding in cases where the uterus shows benign mole need not be regarded with similar concern, though one cannot eliminate the possibility of

later choriocarcinoma in primarily benign trophoblastic pulmonary metastases. This could conceivably explain some of the 7 cases of choriocarcinoma in the Registry in which the patient died of lesions in the lungs and other organs with no evidence of choriocarcinoma in the uterus. In these cases we might postulate the failure of a systemic defensive factor in the presence of an adequate local defensive factor in the uterus.

TABLE VI. HYDATIDIFORM MOLE FOLLOW-UP

Living and well 2 years	63
Living and well 1 year	23
Living and well 6 months	1
No follow-up or follow-up of less than 6 months	28
Dead (see text)	5
Total	120

*Follow-Up.*—As can be seen from our follow-up table (Table VI) 5 of our 120 patients have died, and this calls for explanation.

These are cases C.R. 42, 112, 113, 194, and 269. Cases C.R. 42 and 113 have already been discussed in the section under metastases. Case C.R. 112 was one of hydatidiform mole associated with eclamptic convulsions. Death occurred 18 hours after a hysterectomy, and must, therefore, be labeled an operative death.

Case C.R. 264 also had very severe pre-eclamptic toxemia, and died before the mole could be evacuated. At autopsy hemorrhages were found in the brain, lungs, and other organs, but no trophoblastic tissue could be demonstrated in the sections of the organs. Her death was, therefore, probably due to the pre-eclamptic toxemia.

Case C.R. 194 is of special interest because it is the only case originally registered as benign hydatidiform mole, which subsequently developed choriocarcinoma. The patient was a 17-year-old girl who in August, 1951, had a dilatation and curettage done for hydatidiform mole. In September, 1951, she had a repeat dilatation and curettage for excessive bleeding, and the tissue evacuated again showed only benign mole. After six months' amenorrhea curettage was done in June 1952 because of free bleeding. The curettings this time were very suspicious of choriocarcinoma. A total hysterectomy and left oophorectomy were done in March, 1953. Both the uterus and the left ovary were riddled with choriocarcinoma. X-rays of the chest were negative up to the time of the last operation, but two weeks postoperatively the x-ray showed rather definite small metastatic foci. She died of metastases in September, 1953. The fact that there was a six months' period of amenorrhea prior to the discovery of choriocarcinoma in June, 1952, makes us suspect that the choriocarcinoma may have developed from an intercurrent pregnancy long after the molar pregnancy in August, 1951, though the possibility of choriocarcinoma developing in residual molar tissue in the uterine wall out of reach of the curette must also be borne in mind.

Of the 71 patients in our series in whom the uterus was preserved 11 have since had one full-term delivery, 3 two-full term deliveries and one "several" full-term deliveries. One patient is pregnant at the time of writing, and another has had an ectopic tubal pregnancy.

### Chorioadenoma Destruens

Our material includes, in addition to the 120 frankly benign hydatidiform moles, 34 cases of the intermediate type of lesion most often spoken of by Ewing's original designation of chorioadenoma destruens. As this lesion so often comes into both clinical and pathologic competition with the frankly malignant choriocarcinoma, it seemed necessary for us to include a discussion of its characteristics in our recent paper on choriocarcinoma to which the reader will have to be referred. Since, however, there is a very definite overlap in the clinical and pathologic features of chorioadenoma destruens and benign hydatidiform mole, we may perhaps be forgiven for including a brief comment on the differentiation of the two lesions.

While we do not consider that the term chorioadenoma destruens is a good one, it has been accepted by most writers and seems no more objectionable than others which have been used, such as malignant mole, penetrative mole, invasive mole, destructive mole, etc. Neither Ewing<sup>2</sup> nor anyone else seems ever to have defined it, but we have suggested two chief criteria: (1) an inordinate degree of trophoblastic overgrowth and (2) undue penetrativeness of the trophoblastic elements, including the villi, into the depths of the uterine wall, extending into the peritoneum or into the adjacent parametrium or vaginal vault. Such moles can therefore be locally invasive, but they have little tendency to the distant metastasis which characterizes choriocarcinoma, though there are certainly exceptions to this.

We shall not here again go into details as to the microscopic differentiations of such moles from either the frankly benign ones or from the frankly malignant choriocarcinomas. As contrasted with the former, chorioadenoma destruens shows usually large fields of trophoblast, but even very benign moles with very little trophoblast may show the extreme penetrativeness which constitutes the other criterion of this lesion.

As contrasted with choriocarcinoma, we have laid great stress on the fact that chorioadenoma shows a well-preserved villous pattern, and that with rare exceptions choriocarcinoma shows a complete absence of the villi from which the malignant tumor had its source. In only 1 of our 74 cases were a few villi found. In some cases the diagnosis of chorioadenoma destruens cannot be made until after hysterectomy, but in a good many it can be made presumptively or at least suspected by the occurrence of intra-abdominal hemorrhage or by the findings by palpation of parametrial invasion or the demonstration of vaginal extension. Such clinical features, combined with curettings showing benign moles, with or without trophoblastic overgrowth, but with well-preserved villi, make it almost certain that the lesion is a chorioadenoma destruens rather than a choriocarcinoma, which might otherwise be neglected.

*Hormone Tests in Chorioadenoma Destruens.*—Of the 34 cases of chorioadenoma destruens only 13 had any sort of hormone follow-up.

In 9 cases (C.R. 51, 67, 97, 116, 126, 149, 170, 213, 255) the pregnancy test was negative within two months after hysterectomy. In 2 cases (C.R. 64 and 65) the pregnancy tests did not become negative until three months after hysterectomy.



In C.R. 70 the pregnancy test remained positive for five months after the vaginal evacuation of the mole. During this period the lesion extended into the vaginal wall and laterally to the parametrium, but it regressed spontaneously without hysterectomy.

In C.R. 145 the pregnancy test remained positive nine months after hysterectomy, but for five months after hysterectomy trophoblastic invasion of the right parametrium could be detected clinically. This latter lesion regressed spontaneously and the pregnancy test became negative four months after its discovery.

### **Syncytial Endometritis**

We have in the Registry 29 cases registered as syncytial endometritis. We believe this lesion to be similar to the one called syncytioma by Marchand<sup>5</sup> as far back as 1895, and described by him as a variety of atypical choriocarcinoma. We ourselves have never seen a choriocarcinoma made up of only syncytial elements, nor, to our knowledge, has any one reported a definite neoplasm of this variety, though in an occasional choriocarcinoma a disproportionately large amount of syncytium is seen. In other words, we believe the syncytioma described by Marchand is not a neoplastic lesion, but that it represents a residuum of trophoblastic cells after a normal pregnancy, abortion, or hydatidiform mole. The endometrium or decidua often shows such trophoblastic infiltration, and frequently this migration of trophoblastic cells extends deeply into the myometrium, especially at the implantation area. In the endometrium or decidua, this trophoblastic infiltration is always associated with an inflammatory reaction so that the common designation of syncytial endometritis or deciduitis is justified. Inflammation is not usually present in the myometrium. The infiltration of the cells between the muscle fibers is characteristically in small clumps, narrow columns, or singly, with no necrosis of the surrounding muscle, in contrast with the bulky masses of trophoblastic cells which invade the musculature in choriocarcinoma, with usually considerable hemorrhage and necrosis.

All of our 27 patients with syncytial endometritis are, to the best of our knowledge, still living and well, supporting the view that this lesion could not be a variety of the highly lethal choriocarcinoma. In fully 19 of them, however, a diagnosis of choriocarcinoma had been incorrectly made, and in 15 of these a totally unnecessary hysterectomy was done for this benign non-neoplastic lesion. This alone would seem to justify all the emphasis which we put upon this lesion, especially as it is one which pathologists can learn to differentiate very readily from choriocarcinoma.

*Chief Sources of Error in Microscopic Diagnosis of Trophoblastic Lesion.*—As can be seen in Table VII the lesions most commonly mistaken for choriocarcinoma are benign hydatidiform moles, syncytial endometritis, and chorioadenoma destruens. We have not gone into any detail of microscopic description of the latter lesion because we believe this subject has been amply covered in our previous paper.

The factor most commonly responsible for the wrong diagnosis of choriocarcinoma in benign moles and chorioadenoma destruens is the fre-

quently excessive trophoblastic proliferation shown by these lesions near or in the uterine wall. However, we must stress that in these two lesions well-preserved villi are also present, and their presence even with fairly large collections of trophoblastic cells should always make one lean away from the diagnosis of choriocarcinoma.

TABLE VII. CASES WRONGLY DIAGNOSED AS CHORIOCARCINOMA

	TOTAL NO. IN REGISTRY	NO. OF WRONG DIAGNOSES
Benign mole	120	46
Syncytial endometritis	27	19
Chorioadenoma destruens	34	15
Abortion	5	3
Normal decidua of early ovum	1	1
Degenerating tissue (no trophoblast)	1	1
Total	188	85

One must also remember that in any one section it is possible to obtain a tangential cut of the trophoblastic covering of the villi in such a way as to show only large clumps of trophoblastic cells without any villi. One should not, therefore, jump to a diagnosis of choriocarcinoma, but should examine several other sections to exclude this possibility. As we have stated in our previous paper, well-formed villi are almost always absent in cases of choriocarcinoma. We noted a few villi among large masses of trophoblastic cells in only 1 of our 74 cases of choriocarcinoma.

Another source of error is the tendency to rely too much upon the so-called anaplastic changes in the trophoblast. For reasons we have already mentioned we have found this factor to be of very little help in gauging the benign or malignant nature of the lesion.

The presence of hemorrhagic or trophoblastic nodes in the uterine wall has also apparently been thought by some to be characteristic of choriocarcinoma. In the 49 cases of benign mole in which hysterectomies were performed, no less than 26 of the uteri contain one or more of these nodes. On microscopic examination these nodes were seen to consist of benign residual molar tissue with a variable quantity of old blood. At times, however, these nodes will contain only blood clots and a few scattered atrophic trophoblastic cells. Only when these nodes contain the characteristic large masses of well-preserved trophoblast with no villi can one be justified in calling the lesion choriocarcinoma.

The presence of these hemorrhagic nodes in the vagina in cases of chorioadenoma destruens has also been assumed by some to be indicative of choriocarcinoma. One must remember that this local vaginal invasion occurs in cases of chorioadenoma destruens, as well as in cases of choriocarcinoma, but that in the former villi will often be present in the vaginal lesion as well as in the primary lesion in the uterus.

As we can see in Table VII no less than 19 of our 29 cases of syncytial endometritis were misdiagnosed as choriocarcinoma. We believe that this was because the pathologists concerned confused the infiltration of small clumps or narrow columns of syncytial cells characteristic of syncytial endometritis

with the trophoblastic invasion of choriocarcinoma. One should remember, however, that in the choriocarcinoma the invasion is by bulky masses of trophoblastic cells with usually considerable hemorrhage and necrosis. In syncytial endometritis there is no necrosis of the surrounding muscle and no Langhans cells are present. If these differentiations are remembered we believe this confusion will be cleared up to a great extent.

### Summary

1. This is a report of 120 cases of benign hydatidiform mole, 34 cases of chorioadenoma destruens, and 27 of syncytial endometritis in the Mathieu Memorial Chorionepithelioma Registry.

2. The gross and microscopic appearances of these two lesions are reviewed.

3. Contrary to the findings of some authors, we have been unable to derive much help from the gross and microscopic appearance of evacuated molar tissue in predicting whether a given mole will or will not later develop malignant histologic or clinical characteristics.

4. The lesion called syncytial endometritis is a residuum of normal pregnancy, abortion, or hydatidiform mole, and not an atypical variety of choriocarcinoma. Our follow-up of these cases supports this viewpoint.

5. Once again we stress the frequency with which cases of hydatidiform mole, chorioadenoma destruens, and syncytial endometritis are misdiagnosed as choriocarcinoma. The common sources of error are discussed and we have tried to show how most of these pitfalls may be avoided.

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## A CASE OF CHORIONEPITHELIOMA OF THE LUNG

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**C**HORIONEPITHELIOMA having its origin during pregnancy may be dealt with by the obstetrician and gynecologist. Its evolution and morphology have become so complex, however, that he now has often to call upon specialists in other fields, e.g., the biologist, the pathologist, the radiologist, the surgeon specialized in the removal of metastases to other anatomical regions of the body. Conversely, the gynecologist is sometimes called upon as consultant. This was the situation in which the case now to be reported was seen.

The rarity of the disease makes it nearly impossible for one man or even a group of men of the same opinion to report on any appreciable number of cases. Most of the reviews can only be collections of single reported cases. Any reviewer will remove a number of cases from any previous author's list, producing a discrepancy in the number of available cases.

This discrepancy is perhaps especially evident when we try to evaluate the part played by the hydatidiform mole in the production of chorionepithelioma. Some authors have attributed to the hydatidiform mole the development of all choriocarcinomas. Others have asserted that all hydatidiform moles are destined to degenerate into chorionepithelioma, unless an immediate removal is accomplished. Others declare that the hydatidiform mole, when diagnosed, may already have invaded distant parts of the body.

It is well first to sum up briefly the history of the varying opinions in regard to the morphology and evolution of chorionepithelioma.

### *Historical Data.—*

In 1867, R. Volkman first described what was probably a malignant hydatidiform mole. He called it a "destructive placental polyp." Later Ewing named it a "chorioadenoma destruens."

In 1888, Sanger ascribed a maternal origin to the chorionepithelioma, but in 1894, Gottschalk attributed it to a fetal origin. It remained for Marchand to establish, in 1895, the precise origin by meticulous cytological study of the ectoblastic covering of the placenta.

The cases studied up to this time had all been chorionepitheliomas secondary to uterine pregnancy. It was logical to expect similar relationships for ovarian and tubal pregnancies, such as were actually described in 1902 by Kleinhans and in 1905 by Risel. One must also remember the possibility of the ectopic choriocarcinomas developed in chorionic villi transported outside the genital sphere and tardily developed after a pregnancy or even the menopause.



*Definition.—*

Choriocarcinoma is not easy to define. It could be cited as "... a carcinomatous proliferation of the trophoblast, appearing during or after pregnancy and propagated by the blood stream through the whole body, principally to the lungs, the brain, the liver and the spleen."<sup>9</sup>

These tumors never have any stroma. They appear essentially destructive in their histological characteristics and do not elicit any connective tissue reaction. The difficulty in diagnosis lies in differentiating the proliferations of the normal placenta from those of the choriocarcinoma.

*Origin and Frequency of the Choriocarcinoma.—*

The origin of the choriocarcinoma is most frequently in the uterine cavity. It may occasionally develop on the placenta during pregnancy. Generally it occurs on retained placental debris following delivery after an incomplete curettage.

Statistics vary on the frequency of the chorionepithelioma. In retabulating independent statistics the following proportions appear to be the rule:

- $\frac{2}{5}$  follow hydatidiform mole;
- $\frac{1}{3}$  follow an abortion;
- $\frac{1}{4}$  follow normal pregnancy and confinement.

According to Novak, hydatidiform mole appears once in 2,500 pregnancies and of these only from 1 to 5 per cent become choriocarcinomas. Choriocarcinomas are said, however, to be encountered once in 4,000 pregnancies.

*Clinical Symptoms.—*

It is nearly impossible clinically to diagnose a choriocarcinoma at its onset. The first and most frequent sign is recurring hemorrhage, but this is also characteristic of hydatidiform mole, threatened abortion, or incomplete abortion. The unusual enlargement of the uterus in relation to the history of the duration of the pregnancy should suggest the possibility of hydatidiform mole. The absence of movement of the fetus and the inability to palpate the head, breech, and limbs add to the necessity of considering molar transformation. In such cases diagnosis can readily be confirmed by a simple roentgenogram of the abdomen. It is also well to remember that the recurrence of hemorrhage from one to five weeks following an abortion, a delivery, or a curettage should lead to the suspicion of a transformation into a choriocarcinoma. Polycystic ovaries are frequently associated with hydatidiform mole and choriocarcinoma, but more frequently with the former.

*Hormonal Factors and Biological Tests.—*

The hormonal biological tests are indispensable, although their interpretation is sometimes subject to controversy. If Aschheim-Zondek or Friedman-Brouha tests are carried out systematically after a pregnancy they become negative very rapidly, seldom later than thirty days. In hydatidiform mole, Payne has noted that, in 36 cases, 66 per cent have become negative in less than thirty days, and 95 per cent in less than three months. Moreover, Merger<sup>13</sup> has established the fact that the prolonged persistence of a small quantity of

Prolan B after the expulsion of a mole or a placenta, indicates the persistence of molar remnants or the malignant transformation of mole. This is especially true if the quantitative values are stationary or increasing.

It is imperative to follow these cases regularly, from the clinical point of view, but biological tests must also be made every three or four weeks. It should be remembered that in addition to a normal pregnancy, hydatidiform mole, or a choriocarcinoma, there are some other lesions than can occasionally give a positive Aschheim-Zondek or Friedman-Brouha reaction.

*Indications for the Aschheim-Zondek or Friedman-Brouha Tests.—*

One of these tests should be used in the following instances:

- A. In prolonged hemorrhage after a confinement or an abortion.
- B. Following the expulsion of hydatidiform mole, every three weeks for three months and then every three months for one year.
- C. Following an operation for a choriocarcinoma, on the schedule followed for hydatidiform mole for one year and at yearly intervals thereafter.
- D. In all cases where a tumor of the adrenal cortex or of the anterior pituitary is suspected, or in diseases of the hypothalamus, and in cases with intracranial hypertension.

*Factors Leading to Error in the Aschheim-Zondek or Friedman-Brouha Tests.—*

As in any other laboratory test there are possibilities of error which must be taken into account. Erroneous reports have been encountered due to the following factors: (a) hormonal disorders in the test animal; (b) faulty administration of the hormone; (c) the possibility of the hormone-producing tumor being enclosed in a fibrous capsule preventing the hormone from entering the circulation; (d) degeneration or necrosis of the tumor; (e) faulty renal function preventing the appearance of the hormone in the urine.

*Physiological Metastases of Pregnancy.—*

It has been definitely established that trophoblastic tissues of decidual cells and even villi enter the maternal blood stream and reach the lungs as emboli or metastases, where they may remain in a latent state until the end of the pregnancy. At delivery these metastatic cells or emboli are eliminated by an unknown substance with a specific histolytic power.

Schmorl<sup>8</sup> has found such trophoblastic tissues in autopsies of women who had died of eclampsia or after delivery. Poten<sup>1</sup> goes so far as to state that trophoblastic cells circulate freely in the blood stream in all cases of pregnancy. It is possible that in hydatidiform mole or chorionepithelioma these metastases may occur still more easily.

*Malignancy of the Choriocarcinoma.—*

Choriocarcinoma is considered as the most malignant of all carcinomas of the pelvis. Its dissemination occurs through the blood stream rather than by the lymphatics or through local invasion. The lungs are most frequently involved, followed in order by the brain, the liver, the spleen, and finally the kidneys.

It is difficult to establish accurate statistics on the outcome, for a great number of cures originally reported in malignant cases now seem doubtful as to their malignancy. Most statistics give a 70 to 80 per cent mortality, but Novak<sup>29</sup> is of the opinion that it is closer to 90 per cent if we depend upon the criteria of Hertig<sup>29</sup> for diagnosis.

Metastases are often diagnosed only after death which usually occurs five to six months following delivery. Only rarely do we encounter choriocarcinomas without any trace of the primary lesion. Nevertheless Hoffman, Schmitz, Novak, and others relate a certain number of such cases.

#### *Regression of Pulmonary Metastases.—*

It is difficult to prove the regression of metastases in choriocarcinoma, yet twenty cases have been reported in the literature of which twelve concern pulmonary metastases. Such cases have been cited by Mazer,<sup>14</sup> and Peightal.<sup>15</sup> Although proof is difficult to establish it is possible that following the early removal of the primary tumor concealed metastases may often disappear, as a result of the same histolytic process that produces the disappearance of the physiological metastases after normal pregnancy.

#### *Late Development of Certain Metastases.—*

In most cases, metastases appear a few weeks or at most a few months after the removal of the primary tumor. The Hinglais<sup>34</sup> have insisted that the metastases occur at the same time as the development of the primary tumor and that these may disappear spontaneously following the removal of the tumor if the hysterectomy is done soon enough. Evidence against this theory is found in some cases in which metastases appear, not only many months, but even years after the removal of the primary tumor.

Feiner<sup>16</sup> reports 47 cases with an interval of from 1 to 13 years. Lynch<sup>7</sup> reports one case after 31 years. To explain such cases we must suppose that the histolytic substance did not complete its destructive effect upon the metastases at the time of the removal of the primary tumor. No doubt, some metastases are left dormant. On the occasion of a new pregnancy, or an abortion, or a trauma, or from an unknown hormonal factor, these latent metastatic cells may later be revived.

#### **Case Report**

Maier<sup>27</sup> reported the observation of a woman 32 years of age who developed a choriocarcinoma of the lung three years following a hydatidiform mole. His patient survived for at least three more years after panhysterectomy, lobectomy, and x-ray therapy. In conclusion, the author wrote: "The pulmonary metastases of choriocarcinomas are frequent; they grow rapidly and terminate generally by death. A few cases with pulmonary metastases atypical in evolution were cured by radiotherapy following hysterectomy."

We have personally observed a case similar to that of Maier.<sup>27</sup> Some of the data are incomplete and depend upon reports from a hospital nearly a thousand miles from Montreal.

Mrs. A. L., No. 4306-53, 29 years of age, was admitted to Notre-Dame Hospital, University of Montreal, Faculty of Medicine on April 25, 1953, for a "tumor of the lung" and

directed to the chest clinic. Her complaints were: grippe syndrome with dry and persistent cough over a month; thoracic pains in the right supero-anterior region; asthenia, anorexia, and nausea; nocturnal sweating; and the loss of 7 pounds in weight in the last month.

*Gynecological History.*—

She menstruated for the first time at the age of 15, and had a regular cycle of 30 days until her marriage at the age of 23 years. Thereafter, the cycle was four weeks, the periods having a duration of from 3 to 4 days. On June 24, 1948, she was admitted to the Hôtel-Dieu of St. Joseph of Campbellton, N. B., for uterine hemorrhage following a period of amenorrhea of four months. A roentgenogram of the abdomen showed no visible signs of a fetus. A uterine curettage revealed the presence of a hydatidiform mole which eventually required two more curettages before the bleeding could be stopped. She was discharged from the hospital on July 13, 1948, in good condition.

In the following three years, she gave birth to three normal babies at term. Since her last confinement in March, 1951, she had enjoyed good health except for a prolongation of the menses up to a duration of 6 to 8 days.

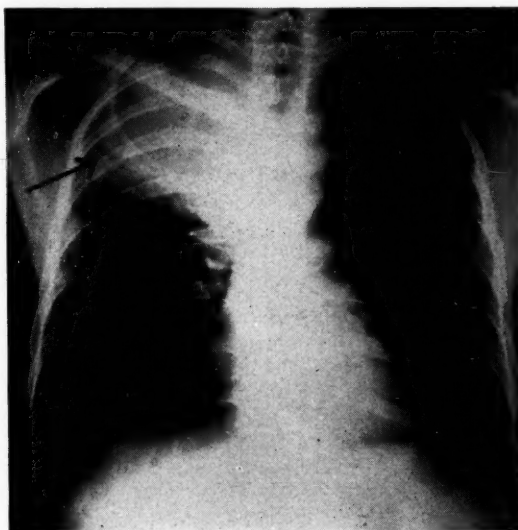


Fig. 1.—Roentgenogram of lungs on arrival. Tumor easily discernible in upper right lobe.

At the beginning of March, 1953, she developed "grippe" with a cough which no medicine could relieve. She consulted her physician who advised a roentgenogram of the lungs which proved to be negative. Her menstruation was then delayed for 10 days. From April 10 to 19 she had profuse uterine bleeding which continued as a reddish discharge. In the third week of April, her cough became more severe. A second roentgenogram now showed a lesion of the right lung which caused her physician to send her to the Chest Clinic at Notre-Dame Hospital.

Upon arrival, the patient appeared tired and pale. Her weight was 103 pounds. The clinical examination revealed an absolute dullness with absence of breath sounds in the right upper lobe. Bronchoscopy revealed an extrinsic obstruction of the bronchus of the apical segment of the right upper lobe.

On April 27, a roentgenogram report read "... presence of a segmentary opacity occupying the apical and anterior segments of the superior lobe. There seems also to exist a thickening of the apical pleura as well as a small effusion at the right base with obliteration of the cul-de-sac. From the past history, this is probably a metastasis. (Dr. J. L. Léger.)" (Fig. 1.)



Called in consultation on April 30, we noted slight bleeding from the uterus. The cervix was eroded, soft, and slightly dilated. The body of the uterus was of normal size and position, mobile, and nonpainful. The adnexa were palpable, slightly enlarged on the right side.

In view of the complex gynecological history, we suggested that there might be a late pulmonary metastasis of a chorionepithelioma. The excessive trauma suffered at the time of the repeated curettages for hydatidiform mole, followed by three successive term pregnancies in three years, may have contributed to the dissemination of trophoblastic tissue in the lung and the late malignant transformation of a condition perhaps primarily benign.

Before confirming or eliminating this possible hypothesis we had a series of qualitative and quantitative Friedman-Brouha tests made. These showed the following:

May 2, 1953—Undiluted: positive;  
May 6, 1953—Diluted 1/10: positive;  
May 8, 1953—Diluted 1/100: positive.

A biopsy-curettage was then carried out, although without much hope of obtaining useful information. The curettings showed a "mucosa at the proliferative stage, the stroma containing lymphocytes, plasmocytes, and polymorphonuclear leukocytes without chorial villi nor choriocarcinomatous debris."

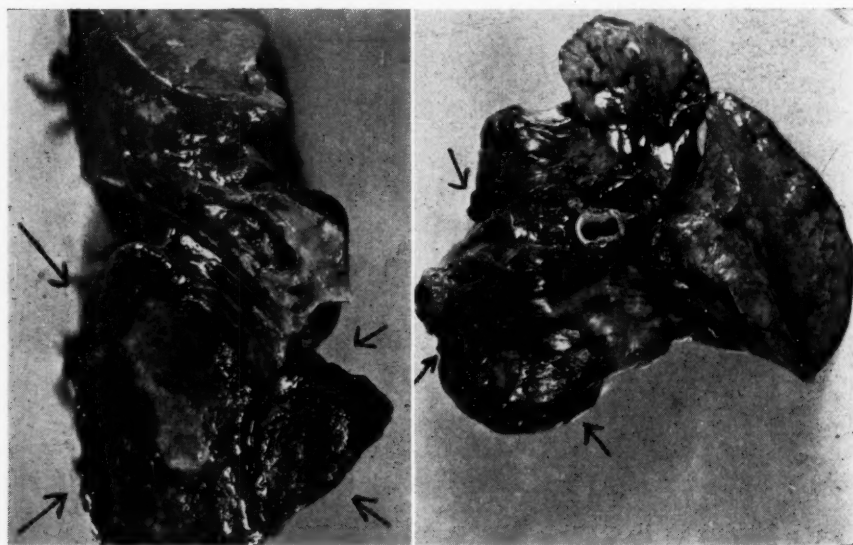


Fig. 2.

Fig. 3.

Fig. 2.—Front view of tumor.

Fig. 3.—Back view of tumor.

On May 16, Dr. Ed. Gagnon performed a right thoracotomy. A very hard mass, adherent to the parietal pleura, was found replacing the superior lobe of the right lung. The tumor was isolated by extrapleural decortication, although the pleura was found to be intimately attached to the superior vena cava. A fragment of the latter was removed for biopsy, and then a pneumonectomy was carried out.

The pathologist's examination of the specimen disclosed the following: The tumor measured 6 by 11 cm., was of a dark red color and very hard consistency. The cut section was multi-colored and hemorrhagic (Figs. 2 and 3). On microscopic examination, the tumor was found to contain numerous areas of necrosis, recent and old hemorrhage, and strands of hyaline sclerosis. The tumor tissue, dispersed throughout these necrotic and hemorrhagic areas, was composed of small, richly vascularized cellular islands. The cells themselves were

acidophilic or nearly colorless, their shape usually polygonal, their nuclei variably shaped. These cellular elements recalled the Langhans cells of the placenta. In most places the capillaries were covered by a normal endothelium, but in a few areas there existed only a blood sinus covered by cells of syncytial type. The diagnosis was choriocarcinoma of the right lung (Fig. 4).

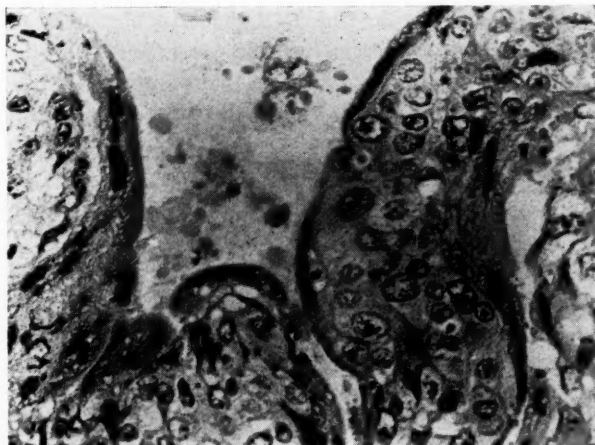


Fig. 4.—High-power photomicrograph showing characteristic choriocarcinomatous cells.

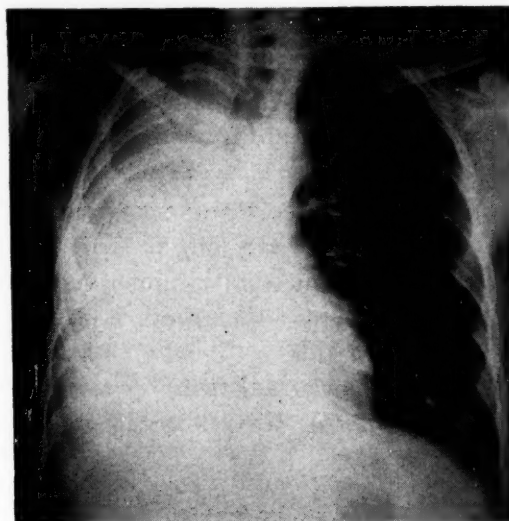


Fig. 5.—Roentgenogram of lungs one month after removal of right lung. Metastases are developing in left lung.

The fragment taken from the superior vena cava was found to be diffusely invaded by similar choriocarcinomatous tissue.

The postoperative course was relatively normal considering the seriousness of the operation and the physical condition of the patient. A week later an undiluted Friedman test was negative. Another made thirteen days after the operation was also negative, but a third one done on the twenty-third day was positive.

A gynecological examination done on the twenty-fourth postoperative day, June 11, left the impression that the ovaries, particularly the right one, were enlarged and might

be polycystic. The general condition of the patient being considerably improved, it was decided to remove the uterus and the adnexa. A total hysterectomy and bilateral oophorectomy were performed on June 15. The exploration of the abdominal cavity showed no visible or palpable metastases.

The pathologic study showed that the uterus measured 8 cm. in length and that the right ovary contained a cyst 4 cm. in diameter. Serial sections of all specimens were studied. No choriocarcinoma was found in the endometrium or myometrium, or in the cervix, tubes, or ovaries. The ovarian cyst was of the lutein type.

Postoperative recovery was again uneventful. Ten days following the operation the undiluted Friedman test was still positive. On June 29 it was positive when diluted 1/10; on July 2, it was positive when diluted 1/100.

Roentgenograms of the lungs had been negative until mid-June, when some metastases appeared in the left lung (Fig. 5). Radiotherapy was attempted but with no success.

On July 5, the patient asked to return home. Her family physician then saw her regularly and wrote to us describing her gradual decline with dyspnea, hemoptysis, general weakness, and pain in the lower limbs. Dyspnea and cachexia became progressively more pronounced and the patient died on Aug. 20, 1953. There was no autopsy. There was no doubt that death was due to lung metastases of a choriocarcinoma.

The special interest of this history lies in the fact that there have been few cases of choriocarcinoma of the lung without the presence of a primary genital lesion.

Since 1942, eight cases of true choriocarcinoma have been seen at Notre-Dame Hospital. The reported case is the only one of the eight that has ended fatally. All the others were operated upon within five weeks from the time of delivery or curettage, save one which was referred 16 weeks after a normal labor. Four cases followed hydatidiform mole, including the one reported here, three followed abortion, and one, a full-term delivery.

Table I is disconcerting. It represents some cases reported in the literature where choriocarcinoma appeared a long time after any known pregnancy. It seems therefore possible for a metastatic tumor to develop tardily. Nevertheless, some authors still maintain that there is always an unknown pregnancy in the days preceding this malignant transformation. It was possibly so in our case, when a menstrual delay of ten days occurred in March before the onset of the final illness. Yet the curettage done a month later gave no evidence of recent pregnancy.

Park and Lees<sup>30</sup> report the appearance of a choriocarcinoma in a woman 55 years of age three years after the menopause. We concur with the hypothesis of Schmorl and Novak<sup>8</sup> that the metastatic elements from the normal placenta have less tendency to proliferate than those of the hydatidiform mole that give evidence of further growth after their distant metastases. It is possible that distant metastasis of the benign hydatidiform mole occurs at the time of the curettage and becomes malignant much later. Alternatively, it is sometimes true, as Mathieu has suggested, that choriocarcinoma develops simultaneously with mole and that it is transported to the lung as a malignant tumor remaining in a latent state for many months or even years after a curettage. The case here reported seems to favor such a hypothesis.

TABLE I. LATE APPEARANCE OF CHORIOCARCINOMA FOLLOWING PREGNANCY. CASES TAKEN FROM DIFFERENT AUTHORS

AUTHOR	AGE OF PA-TIENT	PAR-ITY	TYPE OF PRECEDING PREG-NANCY	INTERVAL BETWEEN DELIVERY AND OPERA-TION	A-Z TEST	PATHOL-OGY AT HYSTER-ECTOMY	A-Z TEST	INTERVAL BETWEEN LAST PREG-NANCY AND OPERATION	RESULT
Dorr and Cutler <sup>12</sup>	70	?	Menopause	?	?	?	?	30 years	Dead. Generalized choriocarcinoma
Brown <sup>20</sup>	22	i	Hydatidiform mole	2 years	?	Negative	?	9 years	Dead. Pulmonary metastases
Cary <sup>3</sup>	37	?	Abortion	5 months	?	Hydatidiform mole	?	3 years	Dead. Generalized metastases
Malcolm <sup>30</sup>	29	?	Hydatidiform mole	?	-	Hydatidiform mole	-	4 years	Dead. Cerebral metastases
Herbert <sup>30</sup>	32	ii	Hydatidiform mole	4 years	-	Negative	+	4 years	Alive after lobectomy for choriocarcinoma
Siegles <sup>40</sup>	24	i	Hydatidiform mole	4 months	-	Choriocarcinoma	+	4 months	Dead. Metastases in lungs, bladder, brain
Siegles <sup>40</sup>	19	i	Abortion	5 months	-	Choriocarcinoma	+	5 months	Dead. Metastases in lungs and brain
Siegles <sup>40</sup>	23	ii	Hydatidiform mole	2½ years	-	Negative	+	2½ years	Dead. Pulmonary metastases
Siegles <sup>40</sup>	33	iii	Abortion	1 year	-	Negative	+	1 year	Dead. Pulmonary metastases
Siegles <sup>40</sup>	38	v	Hydatidiform mole	6 months	+	Choriocarcinoma	+	1 year	Dead. Pulmonary metastases

The choice of treatment varies according to the authors. The Hinglais<sup>34, 37</sup> favor the early removal of the original lesion, by panhysterectomy, in all cases of hydatidiform mole. If metastases are inoperable, radiotherapy should be tried, locally, or as teleroentgentherapy. Others maintain the uselessness of radiotherapy in cases where the risk of operation is too great. Others report some improvement in the symptoms of metastases with the use of estrogens.

### Conclusions

1. There are different degrees of malignancy in hydatidiform mole and choriocarcinoma, which explains the difference in evolution of the disease in different cases.
2. The rare cases of spontaneous regression or cure are due to certain histolytic substances and to the defensive action of the decidual cells.
3. The reported incidence of the change of hydatidiform mole to a malignant tumor varies according to the care with which the histological study is made.



4. Choriocarcinoma may appear at any age between puberty and the menopause or even after the menopause.

5. Multiparas seem more prone to the disease than primiparas.

6. The Aschheim-Zondek and Friedman-Brouha tests have an indispensable value and dilution studies should be carried out for at least 8 weeks following the operation or delivery.

7. The difficulties of interpretation of the curettage are great, for this may yield negative results, even when there is evidence of choriocarcinoma elsewhere in the body.

8. Early diagnosis is most important. Mortality is in direct proportion to the delay in performing the operation.

9. Opinions vary as to the value of radiotherapy.

### Summary

A case is reported of a chorionepithelioma of the lung in a woman who five years previously had had a hydatidiform mole. During the interval between mole and choriocarcinoma there had been three normal pregnancies, the last one two years prior to the appearance of the malignant lesion of the lung. The probable source of the choriocarcinoma and the significance of the latent period are discussed.

I would like here to express my thanks to the members of my staff who took an interest in the case, to Drs. Ed. Gagnon, the chest surgeon, P. Brodeur, radiologist and his staff, L. C. Simard, pathologist and his staff, and Roger Lapointe, my resident, who have been so helpful in the editing of this paper and in allowing me to publish their reports on this interesting case.

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## INTRA-ABDOMINAL RUPTURE OF PELVIC ABSCESES

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THE purpose of this paper is to review the cases of intra-abdominal rupture of pelvic abscesses at the Johns Hopkins Hospital since 1925. The term "pelvic abscess" is used in a broad sense, including tuboovarian abscess, pyosalpinx, and an abscess lying in the pelvis but not enclosed within the tube or ovary. The majority of the abscesses were tuboovarian in type but since the pyosalpinx and extra-adnexal walled-off abscess may also rupture with the same clinical consequences, it was thought advisable to include them in this study.

The study was instigated by our impression that our results in the treatment of the condition have been greatly improved in the past several years. If there has been a real improvement we would also like to know what measures have been responsible for it. We have also attempted to learn the symptoms and signs indicating acute rupture. Although the condition is rare in comparison with the total number of cases of pelvic inflammatory disease, it is by no means uncommon on our service where only the most severe cases of pelvic inflammatory disease are admitted or those on which surgery is planned. Some experienced gynecologists practicing in parts of the country where Negroes are few have never seen a single case of a ruptured adnexal abscess but the complication has been responsible for many deaths on gynecological services in the South. As will become apparent in this study, prompt and proper treatment often spells the difference between life and death.

As a background for the study a short review of the literature is in order. The early literature is concerned chiefly with the report of single cases or a very small number. Lawson Tait<sup>8</sup> reported one case in the years 1868, 1875, and 1883, respectively. In 1889 Boldt<sup>1</sup> described six cases in which the diagnosis was confirmed by autopsy or operation. By 1912 Brickner<sup>2</sup> had collected 91 cases in the literature including his own. In 1925 Lubke<sup>3</sup> reported 34 cases which occurred in the Hamburg Clinic from January, 1900, to November, 1924. Petroff<sup>7</sup> collected 102 cases from the French literature up to 1932 and four years later Ubermuth<sup>9</sup> described 10 ruptured pyosalpinges and 14 ruptured tuboovarian abscesses among 1,730 cases of pelvic inflammatory disease in the Leipzig Clinic. In 1944 Hilliard Miller<sup>4, 5</sup> reported rupture eight times in 500 cases of tuboovarian abscess on the Tulane service at the New Orleans Charity Hospital. The most recent contribution was in 1952 by Pedowitz and Felmus<sup>6</sup> from the King's County Hospital in New York. These authors reported 35 cases occurring in 29 Negroes and 6 whites.

Although this is by no means a complete listing of all reported cases it does indicate that there is a strong preponderance of the condition in the Negro race.

It also shows that it does not complicate pelvic inflammatory disease sufficiently often to gainsay the conservative treatment generally employed.

The seriousness of this complication of pelvic inflammatory disease is best seen by glancing at Table I which records the mortality up to the year 1944.

TABLE I. MORTALITY STATISTICS

AUTHOR	YEAR	CASES	NUMBER DIED	MORTALITY PERCENTAGE
Bonney	1909	45	22	48
Bovee	1910	56	32	57
Brickner	1912	91	56	61
Lamouroux	1912	27	9	33
Lubke	1924	34	14	41
Duval	1929	14	1	7
Petroff	1932	102	28	27
Soimaru	1935	5	1	20
Miller	1944	8	6	75

It has long been recognized that early surgical intervention results in the lowering of mortality. Table II by Petroff justifies this belief.

TABLE II. MORTALITY ACCORDING TO TIME OF OPERATION

HOUR OF SURGICAL INTERVENTION	NO. CASES	NO. RECOVERIES	NO. DIED	MORTALITY PERCENTAGE
Before 12 hours	34	28	6	18
Between 12 and 24 hours	20	15	5	25
Between 24 and 48 hours	9	6	3	33
After 48 hours	11	3	8	73

Past surgical experience has also clearly indicated that simple abdominal drainage carries with it a very high mortality. Pedowitz and Felmus<sup>6</sup> state that the treatment at the King's County Hospital prior to 1947 consisted of medical measures and occasional incision and drainage and the mortality was 100 per cent. Petroff<sup>7</sup> reports 100 per cent mortality in the cases not operated upon and 66 per cent mortality in the cases in which drainage only was carried out. His reported results from various operative procedures are given in Table III.

TABLE III. MORTALITY ACCORDING TO TYPE OF SURGERY

NATURE OF TREATMENT	NO. CASES	NO. RECOVERIES	NO. DIED	MORTALITY PERCENTAGE
Unilateral adnexectomy	29	21	8	27.5
Bilateral adnexectomy	17	15	2	11.8
Adnexectomy and subtotal hysterectomy	22	15	7	30.4
Adnexectomy and total hysterectomy	8	8	0	0

### Present Study

**Material.**—This study is on two groups of cases. Group I includes those cases observed from 1925 to 1944 and Group II those cases seen from 1945 to 1953. This division is made because a decisive change in therapy was instituted in 1945. A more active surgical approach has been used since then and the



patients have had the advantage of modern antishock therapy. A more detailed study has been made of the cases constituting Group II. The Group I cases (1925 to 1944) are considered only as a basis for comparison with Group II as to treatment and results.

*Incidence.*—Although the intra-abdominal rupture of a pelvic abscess is an infrequent complication of pelvic inflammatory disease, it is a serious abdominal catastrophe and the high mortality in improperly treated cases makes the early diagnosis of great practical importance.

There are 22 cases in Group I which occurred in the 20 year interval of 1925 to 1944. There are 25 cases in Group II which occurred in the 8 year interval, 1945 to 1953. This appears to indicate an increased frequency of ruptured abscesses. We believe that this is probably more apparent than real. In the years covered by the first group, there are numerous deaths listed as due to peritonitis complicating pelvic inflammatory disease in which there is not enough information available in the histories to determine whether there was an actual rupture of an abscess. It is probable that many of these cases represent ruptured abscesses, but they are not so indexed and hence could not be included in this series. Also, the hospital now serves a population with a higher percentage of Negro ward patients in whom pelvic inflammatory disease with its serious complications is common. In any case, it seems safe to assume that modern chemotherapy has not reduced the incidence of ruptured abscesses.

During the period covering Group II ruptured abscesses accounted for 3.5 per cent of all the pelvic abscesses treated surgically either by posterior colpotomy or laparotomy.

The average age of the patients was 33 years with the highest number in the fourth decade. This is considerably older than the average age of patients with pelvic inflammatory disease and supports the belief that ruptured abscesses, as a rule, occur after repeated infections or exacerbations of old infections. This age factor is of some importance in deciding whether one is dealing with an initial acute Neisserian infection with peritonitis or peritonitis resulting from the rupture of an abscess from an old pre-existing pelvic inflammatory disease. The former condition can and should be treated safely by nonsurgical methods whereas the latter requires prompt surgical intervention.

TABLE IV. AGE OF PATIENTS WITH RUPTURED PELVIC ABSCESS

AGE (YEARS)	NUMBER
10-19	2
20-29	5
30-39	14
40-49	5

*Race.*—Ninety-two per cent of our cases occurred in the Negro race. Since pelvic inflammatory disease occurs much more frequently in Negroes, we have no evidence to indicate that rupture takes place proportionately more frequently than in whites.

*Pathogenesis.*—Clinical evidence indicates that the underlying pathology of most cases of ruptured abscess is gonococcal pelvic inflammatory disease. Sixty-

one per cent of our patients gave a history of recurring bouts of pelvic inflammatory disease. This fact plus the older age of these patients has led us to believe that the abscess which is likely to rupture is the result of reinfection or exacerbation of an old pre-existing infection. Many of these abscesses have become secondarily infected. In fact, in no instance have we been able to culture the gonococcus. The results of culture are shown in Table V.

TABLE V. CULTURES OF PURULENT INTRA-ABDOMINAL FLUID

ORGANISM	NUMBER
Streptococci	6
Staphylococci	4
Coliform group	4
Negative culture	7
No report recorded	5

These bacteriologic findings probably account for the more serious nature of the peritonitis resulting from rupture of these abscesses than that due to the fresh Neisserian infection.

Other contributing factors were leukemia (two cases) and severe diabetes (two cases).

Two cases occurred in patients who had Pomeroy ligations of the Fallopian tubes, one in the immediate postoperative period, and the other several years later. The ruptures took place in the proximal stubs of the severed tubes. In four cases in Group II, rupture occurred after one or more pelvic examinations and it appeared that the examinations were a contributing factor. One case occurred two years after treatment for carcinoma of the cervix with x-ray and radium, and one was associated with an infected incomplete abortion.

In those cases in which both tubes were removed, there was acute or subacute inflammation present bilaterally in all but one case, indicating that the tubes are the usual source of the infection and that a bilateral salpingectomy is necessary to rid the pelvis of the focus. In 90 per cent of the tubes removed, there was enough purulent material within the lumen to justify a diagnosis of pyosalpinx.

*Symptoms.*—Table VI lists the incidence of the reported symptoms.

TABLE VI. SYMPTOMS OF RUPTURED PELVIC ABSCESSSES

SYMPTOMS	INCIDENCE (PER CENT)
Lower abdominal pain	100
Nausea	90
Sudden onset of new pain or increased severity of pain	80
Vomiting	71
Abdominal swelling	40
Weakness	35
Chills	30
Metrorrhagia	30
Fever (subjective)	25
Feeling of faintness	25
Leukorrhea	20
Constipation	20
Frequency of urination	15
Dysuria	10

Lower abdominal pain was the presenting complaint in all cases. The pain was frequently described as crampy. In 80 per cent of the cases, there was a recognized time of sudden increase in the severity of the pain which usually spread, often into the upper abdomen. Such a history is interpreted by us as the time of rupture. All of the abscesses but two appeared to have ruptured less than 10 days after the onset of lower abdominal pain associated with the supposed exacerbation of pelvic inflammatory disease. Nausea and vomiting were frequently encountered but as a rule the vomiting was of only brief duration. An appreciable percentage of patients noted abdominal swelling, weakness, chills, fever, and feeling of faintness.

*Signs.*—The characteristic signs were those of generalized peritonitis with a palpable pelvic mass. Peritoneal irritation showed itself by the several signs of tenderness, rebound pain, spasm, and in some cases rigidity. Examination for the bowel sounds and free fluid was reported on in less than 50 per cent of the cases but we believe that these valuable signs should be recorded in all cases of acute abdominal crisis. It is of interest that a temperature over 101° F. and pulse over 110 were found preoperatively in practically all cases.

TABLE VII. SIGNS OF RUPTURED PELVIC ABSCESS

SIGN	INCIDENCE (PER CENT)
Temperature over 101° F.	100
Pulse over 110	90
Blood pressure less than 90/70 with clinical shock	25
Pelvic tenderness	100
Pelvic mass	90
Generalized abdominal tenderness	80
Abdominal distention	80
Absent or diminished bowel sounds	70 (when recorded)
Shifting dullness	40 (when recorded)

*Laboratory Findings.*—

*Hemoglobin:* A slight anemia was frequently present but in only two cases was there a hemoglobin of less than 10 Gm. and one of these occurred in a patient with leukemia.

*Leukocyte count:* The white count appeared to be uniformly elevated with an average white count of 17,000. Of two patients with counts less than 10,000, one had leukemia.

*X-rays of abdomen:* Flat films of the abdomen were of value, but were taken in only 50 per cent of the cases. Seventy per cent of the films showed evidence of small bowel distention with usually some gas in the large bowel. Forty per cent of the cases showed evidence of free fluid with a hazy appearance and a loss of psoas shadows.

*Treatment.*—The type of treatment and results in the two groups of cases are tabulated in Tables VIII and IX.

The uncorrected mortality in Group I is 90 per cent and in Group II, 12 per cent. Of the two patients who survived peritoneal drainage in Group II, one required another pelvic operation for inflammatory disease. Of the seven who survived unilateral salpingo-oophorectomy, three were reoperated upon

at a later date for pelvic inflammatory disease. Thus, reoperation was found necessary in 44 per cent of the cases treated surgically by less than hysterectomy and salpingectomy.

TABLE VIII. GROUP I—1925-1944

TYPE OF THERAPY	NO. OF CASES	RECOVERY	DEATH
No operation	7	0	7
Peritoneal drainage	13	2*	11
Appendectomy	1	0	1
Bilateral salpingectomy, oophorectomy, and hysterectomy	1	0	1
Total	22	2	20

\*These two cases were in the same patient who survived two separate ruptures of a pelvic abscess. The patient eventually had a hysterectomy for pelvic inflammation.

TABLE IX. GROUP II—1945-1953

TYPE OF THERAPY	NO. OF CASES	RECOVERY	DEATH
No operation	1	0	1
Peritoneal drainage	3	2	1
Unilateral salpingo-oophorectomy	7	7	0
Bilateral salpingectomy with hysterectomy	13	12	1
Unilateral salpingo-oophorectomy (previous hysterectomy and unilateral salpingo-oophorectomy)	1	1	0
Total	25	22	3

*Time of Death.*—The one patient in Group II who was not operated on was in severe heart failure. It was decided to treat her conservatively. She died 48 hours after rupture of a tuboovarian abscess in spite of full antibiotic therapy. Autopsy confirmed the diagnosis. All seven patients in Group I who were not operated on had the diagnosis confirmed at autopsy. Six of these died less than 60 hours after the apparent time of rupture. It was found that death occurred less than 90 hours after the supposed time of rupture in 88 per cent of the fatal cases, both operative and nonoperative.

*Cause of Death.*—Most deaths appeared to be the result of severe shock from peritonitis and the often accompanying severe paralytic ileus.

Two patients died following treatment by hysterectomy with bilateral salpingo-oophorectomy, one in Group I and one in Group II. The patient in Group I died in shock and was in diabetic acidosis. The patient in Group II died suddenly on the fourth postoperative day presumably from acute gastric dilatation, as she would not tolerate suction. Autopsy was not obtained.

### Comment

The reduction in mortality from 90 per cent in Group I to 12 per cent in Group II has been accomplished by attention to details in all phases of care.

*Prophylactic Phase.*—The proper treatment of all patients with pelvic inflammatory disease should prevent rupture of some abscesses; hence all cases of acute pelvic inflammatory disease should receive full antibiotic therapy and be followed until cured. Cases in which palpable abscesses are present should be closely watched. Preferably, the patients should be admitted to the hospital, but if this is not feasible they should be followed closely while on antibiotic



therapy. If a localized abscess forms, as in the cul-de-sac, it should be drained by posterior colpotomy. Many adnexal abscesses respond to conservative therapy, but, not infrequently, a patient will be encountered in whom the abscesses fail to respond to conservative therapy and in whom cul-de-sac drainage is not possible. Patients with such persistent large abscesses should receive vigorous antibiotic therapy preoperatively and then a planned hysterectomy and salpingectomy or salpingo-oophorectomy. Penicillin will usually conquer the gonococcus but other drugs must be added to take care of the secondary invaders. We have no special preference for any of the broad spectrum antibiotics. We limit streptomycin usage to five days if possible and then change to aureomycin or Terramycin.

*Diagnosis of Rupture.*—The diagnosis is to be suspected in a patient with a history of pelvic inflammatory disease in whom, during a recent exacerbation, there has been a sudden increase in the severity and extent of abdominal pain. Examination usually reveals a temperature over 101° F. and pulse over 110. There are signs of generalized peritonitis with a pelvic mass. Shifting dullness and diminished or absent bowel sounds may be noted. The leukocyte count is likely to be over 15,000. A flat film of the abdomen may reveal dilated loops of small bowel with free fluid in the abdomen. Shock may be present or may develop while the patient is under observation.

A correct preoperative diagnosis was made in 66 per cent of the cases in in Group II. Once the diagnosis is made, a definite plan of therapy is necessary.

*Preoperative Phase After Rupture.*—Operation should be undertaken after rapid, but adequate, preoperative preparation. The patient's blood should be grouped and cross-matched with 1,500 c.c. of blood. The blood transfusion can usually be started as soon as available. Emergency blood chemistry determinations are obtained and intravenous fluids started immediately. Vigorous antibiotic therapy should be undertaken. Penicillin, streptomycin, and intravenous Terramycin are used at this stage because they are given parenterally. An indwelling Foley catheter is helpful in controlling fluid balance. Generally, it is advantageous to pass a Cantor or Miller-Abbott tube before operation. "Combat shock" is the watchword through treatment. It may be necessary when seeing the patient at a late stage to use plasma or a norepinephrine infusion.

*Operative Phase.*—Blood transfusion should be started before surgery. The anesthetic of choice depends to some degree on the preference of the anesthetist but in general we prefer cyclopropane with curare.

The operation should be carried out as rapidly as possible. Although time is not a very important factor in some surgery, it is when dealing with these patients. The patient should not be put in Trendelenburg position until the abdomen is packed off and no more Trendelenburg position than necessary should be used to prevent a dissemination of pus in the upper abdomen. The operation of choice is the removal of the free pus together with the abscess, uterus, tubes, and usually the ovaries. Rarely is it possible to leave some ovarian tissue. Even in the best surgical hands we believe that a subtotal hysterectomy is faster than a total and should be done in these patients. It is probable that the mortality would be increased if total hysterectomy were always

done. Although we in this clinic believe firmly in total hysterectomy we do not believe it should be persisted in when the danger of total hysterectomy exceeds the danger of leaving the cervix in.

As a rule it is much easier to remove the corpus in these cases than to attempt a unilateral adnexectomy. Furthermore, the opposite adnexa are almost always involved and subsequent operation may be necessary if conservation of one side is practiced. If hemostasis is poor or if there is considerable necrotic material left behind, there may be some benefit from peritoneal drainage with cigarette drains through a stab wound or the cul-de-sac. In any event, after closure of the peritoneum and fascia, a small gutta-percha wick should be put in the subcutaneous fat. The pus from the abdomen should be cultured and the organism tested for sensitivity to the various antibiotics.

*Postoperative Phase.*—In the postoperative care, one should consider shock, infection, ileus and fluid balance.

Shock should be combated with whole blood and if necessary norepinephrine intravenously. We occasionally have had to use an infusion of norepinephrine for many hours to combat shock. Infection is usually controlled by penicillin, streptomycin, and intravenous Terramycin until the patient can take oral medication. The Fowler position may help prevent subdiaphragmatic abscess formation.

Constant suction by means of a Cantor or Miller-Abbott tube is a very important feature of postoperative care. Adynamic ileus is often present and is best treated with the long tube.

Close attention to fluid balance and blood chemistry determinations is necessary. Not infrequently these patients have poor kidney function and the fluid output and nonprotein nitrogen should be closely followed.

### Summary

Intra-abdominal rupture of a pelvic abscess is a serious complication of pelvic inflammatory disease but not so frequent as to indicate operative treatment of all cases of pelvic inflammatory disease. A modern method of treatment has been presented that has lowered the mortality from 90 to 12 per cent at the Johns Hopkins Hospital. Vigorous treatment of shock, antibiotic therapy, deflation of the distended stomach and bowel by the Cantor or Miller-Abbott tube are important preoperative measures. Removal of the pelvic source of infection by subtotal hysterectomy with bilateral salpingo-oophorectomy is usually the operation of choice. This should be done promptly and followed by continued therapy of the type instituted preoperatively.

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## THE TRANSVERSE INCISION IN PELVIC SURGERY

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THE longitudinal or vertical incision of the abdominal wall—the time-honored “lower midline incision”—has long been the incision most commonly employed in the abdominal approach to pelvic surgical procedures. This incision has certain recognized advantages which have led to its universal acceptance as the incision of choice by the majority of obstetrical and gynecological operators. However, this widespread use has often appeared to be dictated more by custom than by reason. As early as 1823, Baudelocque<sup>1</sup> proposed a “nouveau procédé” for performing the cesarean operation which advocated the use of a transverse abdominal incision. Pfannenstiel<sup>2</sup> in 1900 popularized the low transverse incision which bears his name, and Maylard<sup>3</sup> in 1907 advocated the additional feature of cutting the rectus muscles when fashioning these incisions. In 1916, Moschcowitz<sup>4</sup> elaborated and clarified the sound anatomic and physiologic principles upon which transverse incisions are based, and since that time numerous investigators have confirmed and amplified these basic tenets. In the last two decades, many articles have appeared in the literature urging the routine use of the transverse incision.<sup>5-11</sup> It is our feeling that this incision is the one of choice in pelvic surgery.

### General Considerations

The surgical approaches to the abdominal viscera by means of incisions through the abdominal wall have been developed upon certain general basic principles:<sup>12</sup> (1) Incisions should give ready access to the part to be investigated. (2) They should be sufficiently extensible as to allow for reasonable enlargement of the scope of the operation. (3) They should interfere as little as possible with the functions of the abdominal wall, both in the immediate postoperative period and later when normal activities are resumed. (4) Closure of the wound must be anatomically and structurally reliable. (5) A good cosmetic result should be obtained when time and circumstances permit.

The vertical midline incision has most readily adapted itself to general use for pelvic surgery. Most of the basic principles just enumerated are fulfilled to some degree by this incision. It has the advantages of being easily and rapidly fashioned. In addition, it may be extended upward with comparative ease, thus increasing the degree of exposure and permitting an extension of the field of operation. There is little bleeding associated with the making of the incision, since it is performed through a relatively avascular aponeurotic layer and does not cut across any major blood supply. Moreover, closure of the wound is technically not difficult.

A review of the anatomic and physiologic considerations involved when the components of the abdominal wall are incised, however, lends doubt to the validity of many of the advantages claimed above. It first must be realized that the rectus sheath is not a vertical tendinous component of the fibers of the rectus muscle, paralleling the latter. In reality, the rectus sheath is formed by the transversely proceeding aponeurotic fibers of the three flat muscles of the abdominal wall (internal oblique, external oblique, and transverse abdominis).

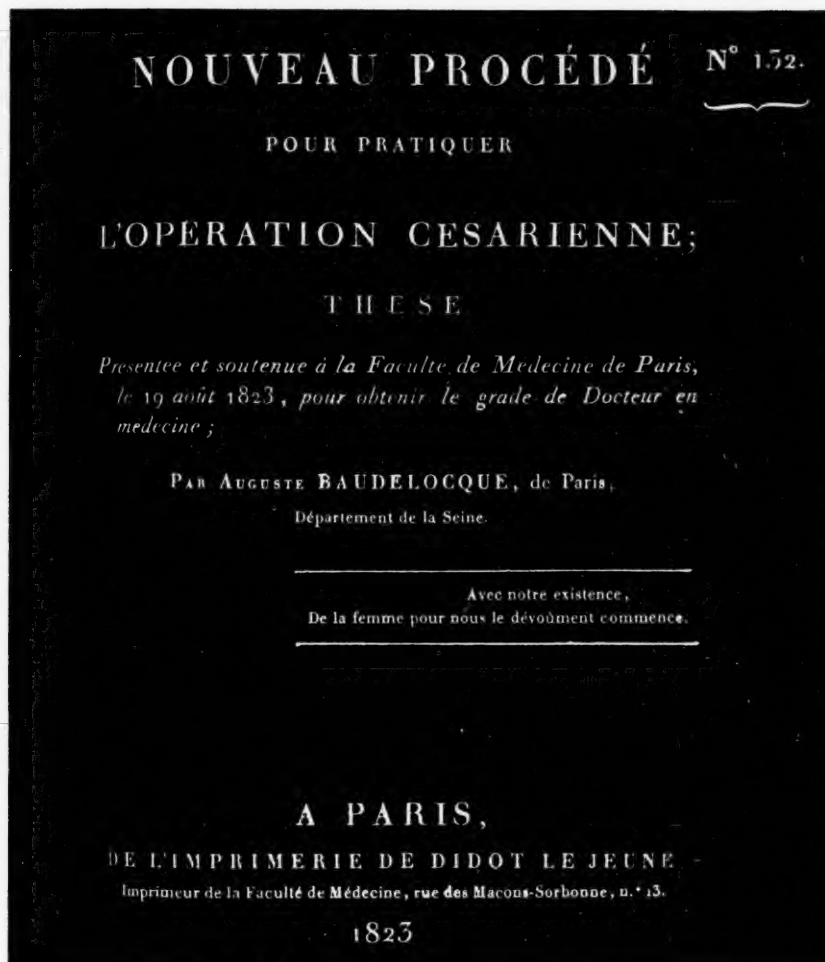


Fig. 1.—Title page of Auguste Baudelocque's thesis presented in 1823 to the Faculty of Medicine of Paris, in which he advocated the use of the transverse abdominal incision for cesarean section.

These fibers are in point of fact the tendons of the latter muscles; these tendons find their insertion in the linea alba and take their point of action in that structure.<sup>13</sup> It is apparent then that a vertical incision through the rectus sheath, or through the linea alba, must cut directly across the multiple tendons of the flat muscles. Above the semicircular line of Douglas (which usually lies 3 to 5 cm. below the umbilicus) the rectus sheath is divided into anterior and



posterior components; the anterior portion is composed of aponeurotic fibers of the external oblique and the anterior lamella of fibers of the internal oblique, while the posterior portion is composed of the posterior lamellar fibers of the internal oblique and the tendinous fibers of the transversus abdominis. Thus, the fibrous portion of the internal oblique, as it proceeds to its insertion in the linea alba, splits at the lateral border of the rectus muscle on each side to ensheath the latter. Below Douglas' line the aponeurotic fibers of all three flat muscles pass anterior to the rectus muscle, so that there is in reality no posterior rectus sheath in this area. Here the rectus muscle is separated from the peritoneum only by the deep epigastric vessels, the transversalis fascia, and the peritoneal connective tissue.

The rectus muscles are segmental muscles, with a segmental nerve supply. Three (occasionally four) transverse tendinous inscriptions are found in each muscle; these inscriptions are intimately fused with the anterior rectus sheath of the corresponding muscle. Because of these firm aponeurotic attachments of the muscle to the sheath, there can be only minimal retraction of the muscle fibers when the rectus is cut transversely.<sup>14</sup> Rosenblatt and Colver<sup>15</sup> have further shown in dogs that when the rectus muscle is incised transversely, it heals by the formation of a transverse band of fibrous tissue which is in essence an additional tendinous inscription. This is true when only the rectus sheath is closed, and suturing of the muscle is not required.

The nerve supply to the anterior abdominal muscles arises from the lower six intercostal and first lumbar nerves. Davies<sup>16</sup> and Rees and Collier<sup>17</sup> have shown that there exist rich anastomoses among these nerves between the flat muscle layers; when the nerves reach the lateral border of the rectus sheath they fan out transversely beneath the rectus muscle, being distributed to its deep surface. Once the nerves have reached the sheath, little if any anastomosis occurs. Thus, any incision which passes vertically through the rectus muscle or through its lateral border must denervate that portion of the muscle medial to the incision. Conversely, transverse incisions through the rectus muscle result in the least possible damage to its nerve supply.

Among considerations attendant upon making incisions through the abdominal wall, of importance are those associated with the blood supply to the incised area. A good blood supply with rich anastomoses ensures good healing. The main blood supply to the lower abdominal wall lies in the inferior epigastric artery, which is a branch of the external iliac artery. There is rich intercommunication of the inferior epigastric with the superior epigastric artery, as well as with the deep circumflex iliac, intercostal, and lumbar arteries. However, there is very little anastomosis across the midline, and the linea alba is provided with the poorest blood supply of any area in the abdominal wall. This latter fact may at times contribute to deficient healing of a wound made in this area. It would appear that these anatomic considerations involving muscle, fascia, nerve and blood supply are all of importance in fashioning incisions through the abdominal wall.

Physiologic principles which enter into consideration when the anterior abdominal wall is incised are related primarily to the function of respiration, and secondarily to muscular activity occasioned by such acts as vomiting, coughing,

micturition, and defecation. In this regard it is important to realize that alterations in intra-abdominal volume and pressure are primarily the function of the oblique muscles by virtue of their posterolateral origins and their insertion into the midline linea alba, which is not a fixed point. During expiration the diaphragm is elevated and the anteroposterior diameter of the abdomen is decreased by contraction of the oblique musculature. During inspiration the diaphragm descends and the anteroposterior diameter of the abdomen increases through the agency of relaxation of the oblique musculature. This alternate increase and decrease of the anteroposterior diameter of the abdomen in the postoperative patient goes on eighteen to twenty times per minute. When the tendons of the oblique muscles (rectus sheath) are transected, the abdominal phase of respiration is interfered with to a point where vital capacity is diminished significantly. In addition, strong contractions of the oblique muscle are necessary during the acts of coughing, vomiting, and defecation.

The rectus muscle, on the other hand, is one of locomotion and occupies a very prominent anatomic location in the abdomen, but has little to do with respiratory movements, inasmuch as it is fixed at two bony points (symphysis pubis and lower ribs). Significant contraction of this muscle results in approximation of the thorax to the trunk, such as in bowing. It is also effective in attaining the sitting position from one of recumbency. Experimental and clinical studies have shown that this muscle plays only a minor part in the alterations of abdominal pressure associated with breathing, coughing, defecation, and so forth. The natural reluctance of surgeons to incise the rectus muscle transversely has usually been based upon an erroneous concept that the rectus is comparable to muscles of the extremities; the latter, however, have an axial nerve supply whereas the former has a segmental nerve supply, as has been noted. Transection of muscles such as the biceps and quadriceps results in paralysis of the segment distal to the line of incision; the same is true of the rectus muscle only if it is incised vertically, as in a paramedian longitudinal incision.

### Advantages of the Transverse Incision

The advantages of the transverse incision in pelvic surgery are related to the fundamental anatomic and physiologic principles previously discussed. It is well to analyze the advantages in more detail in the light of accumulated clinical experience.

1. Utilization of the transverse incision results in a lower incidence of certain postoperative complications. Foremost among the latter are wound disruptions and incisional hernias. Farris,<sup>12</sup> from cumulative data comparing 1,060 transverse incisions with 603 vertical incisions for similar operations on the same service, deduced that wound disruption was *five* times more frequent with the latter (vertical) incision. In addition, incisional hernias were *two and one-half* times as common under these circumstances. The only assayable difference between these groups of cases was the type of incision.

Thompson and associates<sup>18</sup> in their series found that the incidence of wound disruption associated with the vertical incision was 3.5 per cent, whereas the incidence associated with the transverse incision was 0.5 per cent. Whitaker<sup>19, 20</sup>

reported only nine wound disruptions occurring in 1,000 consecutive operations employing the transverse incisions; he stated that the incidence of postoperative hernia was definitely lower than in the series of vertical incisions. Hunter<sup>21</sup> feels with Hartzell and Winfield that wound disruption is "essentially a complication of the vertical incision." King<sup>22</sup> states that hernia never results following the use of the transverse incision. This has been the general clinical experience of those utilizing this approach to abdominal surgery.

In addition to the basic anatomic and physiologic concepts, the work of Sloan<sup>23</sup> has served to explain the mechanism whereby wound dehiscence and disruption should be reduced following the transverse incision. By attaching spring balances to mouse-tooth forceps which in turn were attached to the abdominal aponeuroses, Sloan was able to measure the force necessary to hold the edges of various types of incisions together with the patient under light general anesthesia. In every case he found that the lateral force necessary to approximate the edges of a vertical incision was thirty times greater than the vertical force necessary to bring the edges of a transverse incision together. In addition he noted that the longer the vertical incision the greater was the force necessary to approximate the edges; the force required increased in proportion to the square of the length of the vertical incision. This was not true of the transverse incision.

Postoperative complications other than those associated with the incision per se also are reduced by the use of the transverse incision. Thus, the lack of interference with breathing and coughing allowed by the incision has lowered the incidence of pulmonary complications such as atelectasis, pleuritis, and pneumonia. Rees and Coller<sup>17</sup> found the incidence of such pulmonary complications to be 2.6 per cent in a series of transverse incisions, while it had been 9.5 per cent for a comparable series utilizing the vertical incision. The incidence of peripheral venous complications (phlebothrombosis and thrombophlebitis) and resultant pulmonary emboli may be reduced by the free movement in bed and early ambulation which are more readily permitted by the transverse incision. These advantages are in turn due to the minimal amount of pain and the increased inherent strength of the transverse type of scar.

2. The transverse incision allows for more adequate exposure of the operative site than does the vertical incision. This is especially true in pelvic surgery. Gurd,<sup>6</sup> Lee,<sup>7</sup> Pernworth,<sup>9</sup> DeCarle,<sup>24</sup> and others have emphasized this feature. Hunter<sup>21</sup> notes that with a vertical incision the open wound must be stretched into a transverse aperture for most pelvic procedures. Tollefson<sup>11</sup> points out that the transverse incision is completely utilized for exposure, whereas in the case of the longitudinal incision the upper half of the incision is fashioned only to make the lower half more effective to retraction. The wider lateral exposure obtained with the transverse incision not only allows for easier operability on the pelvic organs, but also permits the intestines to be packed off with greater facility.

In regard to exposure, it should be pointed out that at one time an advantage of the vertical incision had to do with this factor. Thus, it has been noted that the vertical incision could be extended upward or downward with

ease, thereby enlarging the field of operation. With the development of more definitive methods of diagnosis and more accurate localization of disease processes, this advantage has largely been dissipated. Less commonly today is surgery performed on an "exploratory" basis with subsequent need for extending an original incision.

3. A stronger and less painful scar is found to result from the transverse incision. This advantage is of course related to the anatomic principles related previously. The skin components of this incision follow and parallel the well-established lines of Langer, thereby reducing to a minimum the damage and irritation inflicted upon the cutaneous nerves. The nature of the blood supply to the abdominal wall, as previously described, ensures the maximum degree of healing when the wound is placed transversely; only where the incision crosses the linea alba is there any relative avascularity.

It has been repeatedly demonstrated clinically that the rectus muscle may be incised transversely with impunity.<sup>5, 12, 17, 18</sup> The previously cited findings of Rosenblatt and Colver<sup>15</sup> on the rectus muscles in dogs have been found to hold true in human beings. The muscles heal by the formation of a transverse fibrous scar, without resultant weakening or distortion of the abdominal wall. The muscles need not be sutured to accomplish such healing.<sup>12, 17</sup>

4. Certain other advantages for the transverse incision are claimed by various authors. DeCarle and Durfee<sup>24</sup> felt that a transverse type of incision in the lower abdomen resulted in an increased degree of safety when spinal anesthesia is used, since less of the anesthetic and muscle-relaxant drugs was needed with the lower level of anesthesia. With the seeming increase in the incidence of cardiac arrest occurring in surgical patients this could be an important consideration.

Most authors have noted that the tendency toward formation of adhesions is greatly diminished with the transverse incision. This is apparently due to two main factors: (1) There are fewer small breaks in the peritoneal closure with this incision, since there is less tension on the sutures as noted above; and (2) the small intestines are usually centrally located about the umbilicus and down the upper half of a longitudinal incision, but above a transverse one.

#### **Disadvantages of the Transverse Incision**

The disadvantages of the transverse incision in pelvic surgery are not many. The most common one relates to the increased time required to fashion this incision in comparison with the vertical incision. This objection may be a valid one under certain rather infrequent circumstances in which extreme haste in entering the abdomen is the primary consideration; such circumstances are admittedly rare. This disadvantage is compensated for to some degree by the greater ease experienced in closing these wounds, with a consequent saving of time.

Other asserted disadvantages relate to the increased bleeding often encountered in making the transverse incision, and the natural resistance to cutting the rectus muscles. The former consideration finds its source in the increased vascularity of the lateral abdominal areas; the epigastric vessels must



frequently be ligated or they may bleed furiously. However, as pointed out in the anatomic discussion, the anastomosis is rich, and this very vascularity ensures firmer and more sure healing of the abdominal wound. Objections to transecting the rectus muscles have no basis in fact.

It has been claimed that the hernias following the transverse incision are much more difficult to repair. This we believe to be true if a Cherney modification has been utilized, and we do not recommend this type of incision. It will be recalled that Cherney<sup>25</sup> advocated freeing the rectus muscles at their tendinous attachments to the symphysis pubis and retracting them upward for exposure. It is our feeling that this incision may be of value in some urologic procedures, but is far inferior to the true transverse approach with cutting of the rectus muscles for pelvic surgery.

The Pfannenstiel incision has many of the advantages of the true transverse abdominal incision, especially in relation to wound healing and cosmetic result. However, it suffers from the serious disadvantage that surgical exposure is definitely restricted by the separated but uncut rectus muscles.<sup>24, 25</sup> In addition, the transversalis fascia and peritoneum are usually incised longitudinally, with the result that the objections previously enumerated pertaining to suture tension and wound healing come into play. We feel that these disadvantages outweigh any theoretical objections to cutting all layers of the abdominal wall transversely.

### Technique

The following technique has been developed for the performance of abdominal pelvic surgery, including cesarean section. It will be noted that various modalities have been adopted, supplementing the basic transverse approach. It is our feeling that all these features have contributed to the general benefits of the transverse abdominal incision. They will be discussed in more detail as the technique is described.

1. The incision is placed at a level marking the junction of the lower one-third and the upper two-thirds of a line from the symphysis pubis to the umbilicus (Fig. 2, *upper*). This plane is usually just below a transverse line joining the anterior superior iliac spines. The incision may be curved slightly if desired. It will be noted that this incision is placed higher on the abdominal wall than the Pfannenstiel incision, being above and out of the pubic escutcheon.

2. Skin and subcutaneous bleeding is controlled by means of electrocoagulation of the bleeding points. This feature results in a minimal amount of tissue destruction. It further permits the exclusion of catgut or other ligature material from these tissues, thereby practically eliminating the incidence of subsequent serum drainage from these wounds, in our experience. A very high frequency current, the "cutting" current, is used for this coagulation and an attempt is made to grasp only the bleeding vessel in the clamp, thus further reducing tissue destruction and reaction.

3. The abdominal fascia is incised transversely (Fig. 2, *lower*). The rectus muscle on either side is freed from its bed by placing the fingers beneath the body of the muscle and bluntly dissecting (Fig. 3). The muscle is then incised transversely (Fig. 4). This section of the rectus may be partial, or through the entire width. Usually the deep (inferior) epigastric vessels on either side can be separated from the dorsal aspect of the lateral border of the rectus and gently retracted from the field of surgery (Fig. 5). However, in approximately

one-third of cases it is necessary to ligate and incise these vessels for exposure. Fine silk (No. 0000) suture ligatures are used on these and other muscle-layer bleeders.

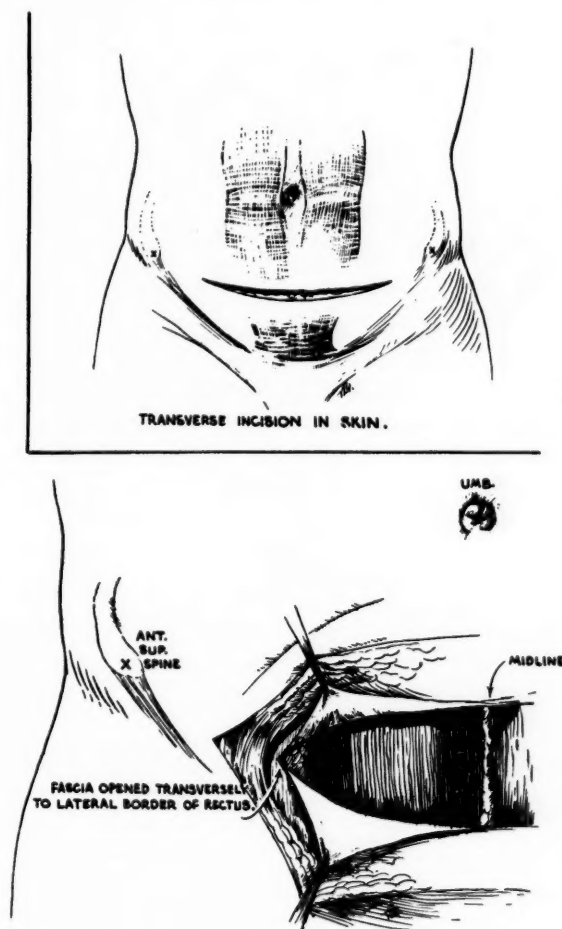


Fig. 2.—Technique of the transverse abdominal incision for pelvic surgery. *Upper:* Location of the skin incision. *Lower:* Transverse incision of the abdominal fascia.

4. The peritoneum is incised transversely (Fig. 6). Bleeding points here are again controlled by electrocoagulation.

5. The abdomen is then thoroughly explored, and the stomach, liver, gall bladder, both kidneys, and the large bowel are gently palpated. (This is a feature which is, unfortunately, all too frequently omitted by the gynecological operator.) A self-retaining retractor of the O'Sullivan-O'Connor type is then placed. Fig. 7 illustrates the retractor in place, and demonstrates the wide lateral exposure afforded by this incision. When cesarean section is performed, exploration of the abdomen and utilization of the self-retaining retractor are omitted.

6. Closure of the transverse incision is facilitated by the natural tendency of the wound edges to fall together. The mechanics of the closure are as follows (Fig 8): (a) The peritoneum is closed with a continuous No. 00 chromic suture. (b) No approximation of the rectus muscle is attempted. (c) The fascia is closed with interrupted sutures of No. 32 stainless steel wire. These

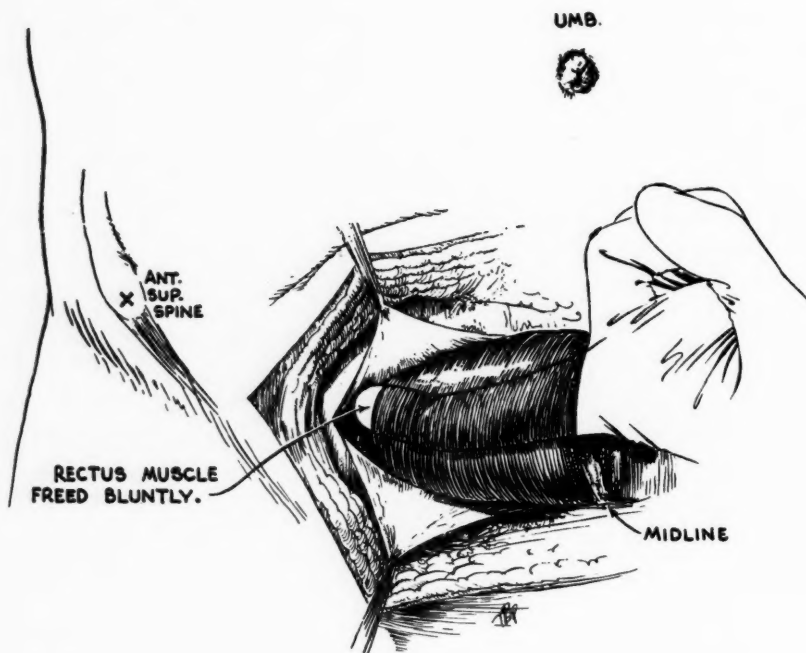


Fig. 3.—Technique of the transverse abdominal incision for pelvic surgery. Blunt dissection of the rectus muscle.

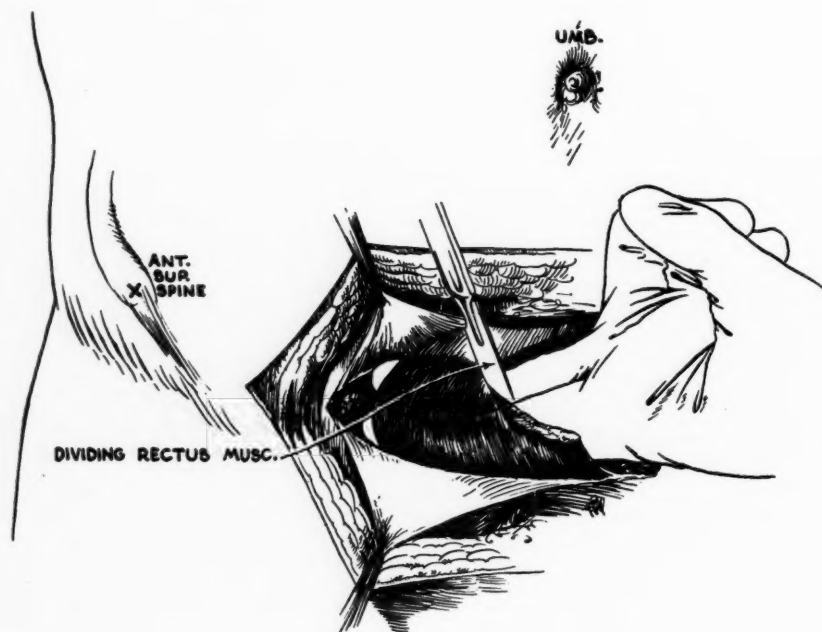


Fig. 4.—Technique of the transverse abdominal incision for pelvic surgery. Incision of the rectus muscle transversely.

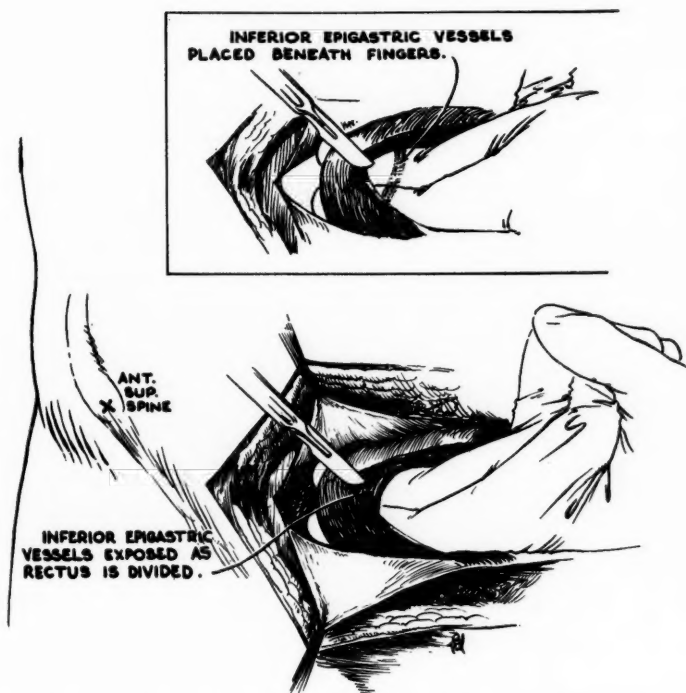


Fig. 5.—Technique of the transverse abdominal incision for pelvic surgery. *Upper:* Displacement of the inferior epigastric vessels dorsally as the rectus muscle is incised. *Lower:* Exposure of the inferior epigastric vessels when they cannot be displaced dorsally. In approximately one-third of cases ligation of these vessels may be required.

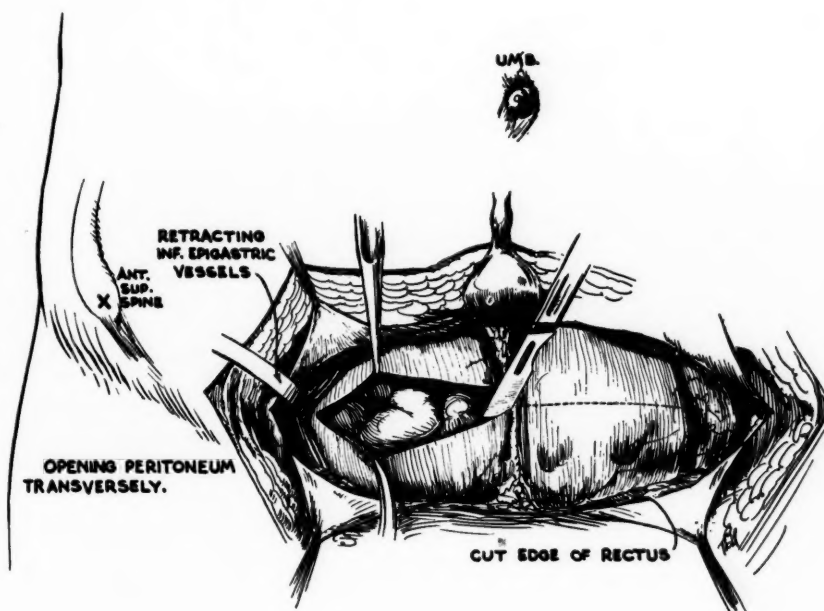


Fig. 6.—Technique of the transverse abdominal incision for pelvic surgery. Transverse incision of the peritoneum. The inferior epigastric vessels are shown retracted from the field.



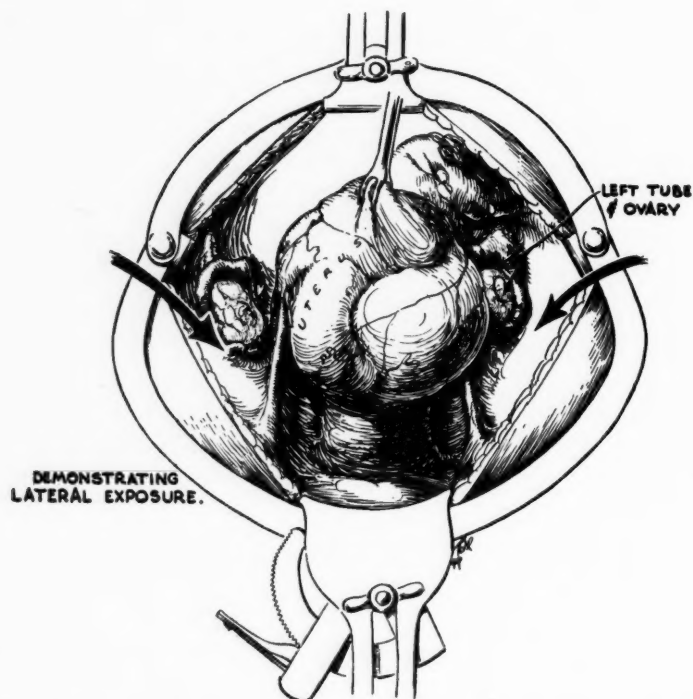


Fig. 7.—Technique of the transverse abdominal incision for pelvic surgery. Illustrating the abdomen open and self-retaining retractor in place. Wide lateral exposure is emphasized.

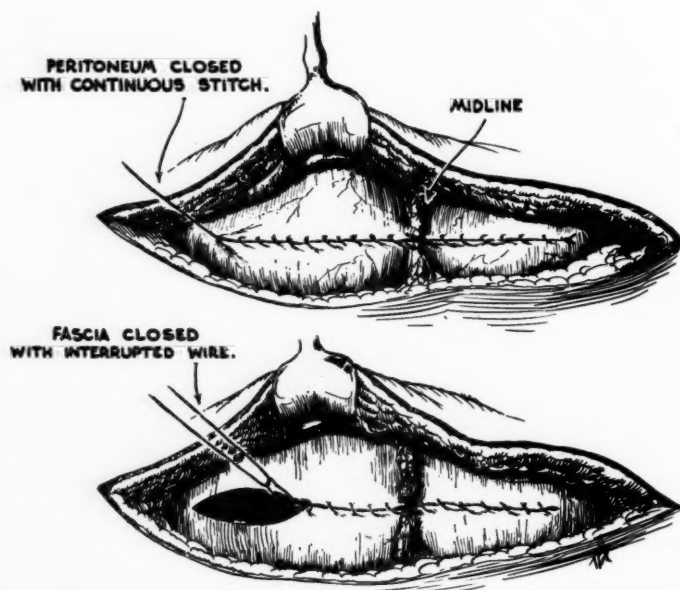


Fig. 8.—Technique of the transverse abdominal incision for pelvic surgery. *Upper:* Closure of the peritoneum with continuous chromic suture. *Lower:* Closure of the fascia with interrupted wire sutures, so placed that the knots are on the dorsal surface of the fascial layer.

wires are so placed that the knots are on the internal (dorsal) aspect of the fascial layer (Fig. 8, *lower*). This prevents any possible irritation of the under-surface of the skin by the cut ends of the wire sutures. It is important to make certain that the lateral angles of the fascial incision are thoroughly approximated. (d) No sutures are placed in the subcutaneous layer. (e) The skin is closed with a continuous subcuticular suture of steel wire (No. 28) or chromic catgut (No. 0000). If wire is used, it is removed on the fifth postoperative day. (f) A very light dressing, if any, is applied.

### Personal Experience

For the purposes of this report we have reviewed 621 gynecological laparotomies and cesarean sections performed on our service utilizing the above technique. The interval of study has covered the period from 1947, when we first began using this incision, through 1952. Thus, there is at least one full year follow-up on the most recent cases, and as long as six years' follow-up on many of the earlier cases. Table I indicates the various types of major surgical procedures performed in these 621 cases.

TABLE I. TYPES OF MAJOR SURGICAL PROCEDURES

Total hysterectomy	228
Supracervical hysterectomy	46
Other gynecological laparotomies	95
Cesarean section	236
Cesarean hysterectomy	16
Total	621

A careful analysis of the various wound complications has been carried out on this series of cases. Table II indicates the incidence found. Seroma refers to serous drainage from the incision and in all cases was superficial and minor in extent. The majority of these occurred in those cases in which subcuticular catgut was used to close the skin, and for this reason we have reverted to continuous wire closure for the cutaneous portion of the incision.

TABLE II. WOUND COMPLICATIONS

Seroma	23
Wound infection	6
Hematoma	3
Hernia	2
Wound dehiscence or evisceration	0

The two hernias occurred among the 6 patients suffering from wound infections. Both patients were found to have pelvic inflammatory disease complicating fibromyomas, and both were operated upon the same morning. One hernia has required subsequent surgical repair; the other hernia is comprised of a small defect at the outer angle of the incision and surgery has not appeared warranted after an observation period of two years.

There were no instances of evisceration in this series.

Certain minor complications which occur with the technique described above may be noted. If the interrupted wire sutures are not cut close to the twisted knot an occasional one may require later removal. This can usually

be done under local anesthesia. We encountered 6 instances in this series in which such removal was necessary, 5 of which occurred during the first year we used wire. In addition we have noted 4 patients who have complained of sensitive wounds and 4 in whom there was induration of the wound, but no drainage.

During the period covered by this study, we have also utilized the lower midline incision in some cases. This has been done for cosmetic reasons presented by certain patients with previous midline scars, or whenever it was felt that the transverse incision might be contraindicated. However, we have not hesitated to use the transverse incision even in the presence of a pre-existing midline scar when a choice was permissible.

### Summary

A discussion of the use of the transverse incision in pelvic surgery is presented. The anatomic and physiologic bases for the advantages of this incision are discussed and the technique, including cutting of the rectus muscles, described. Personal experience with 621 cases in which this incision was utilized is reviewed.

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## HYSTERECTOMY

### The Evolution of the American Attitude Toward the Indications and Types

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THE indications for hysterectomy have remained more or less static in this country for the past half century. During this same period, there has been a gradual but continuing swing toward the use of total abdominal hysterectomy and to a lesser degree toward vaginal hysterectomy.

The obvious gauge of the American attitude is the popularity and frequency with which a gynecologic procedure is employed. Even a casual perusal of the literature of this period will demonstrate the increasing use of total abdominal hysterectomy and the constantly shrinking instances of subtotal hysterectomy. The major gynecologic clinics now report an incidence of subtotal hysterectomy of less than 5 per cent. Actually, each subtotal hysterectomy in these clinics represents a surgical compromise, for this operation is now performed only when the pathology present is of such a nature that it is neither safe nor feasible to carry out total abdominal hysterectomy.

By request of the Editors, this discussion will be concerned only with the period of the active career of Dr. Kosmak and more particularly the period of his illustrious Editorship.

Hysterectomy, in the memory of many of us, was an unusual and spectacular operation and was performed originally only by a few well-trained, skilled, and daring gynecologists. Today, with the more or less universal gynecologic surgical training and with the marked improvements in surgical techniques, anesthesia, blood transfusion, and the control of infection, it is no longer in the realm of the spectacular.

The actual techniques for the various types of hysterectomy can be mastered by anyone who has the opportunity, the time, and the willingness. It is no trick to learn the techniques. The trick involved is the mastering of the knowledge of the indications and contraindications. This takes time, training, and the development of sound, gynecologic judgment. For involved in the attainment of proper judgment must be a knowledge of the effects of hysterectomy upon the individual concerned. These effects are physical, endocrine, and psychic, and they vary both singly and in combination according to the time of life in which the hysterectomy is performed. Hysterectomy before childbearing, during the childbearing years, after the family is complete, and/or in the postmenopausal period varies greatly in the effects produced upon the patient.

The indications for hysterectomy are found primarily in those forms of uterine pathology which require removal of the uterus for their correction or cure. These include uterine malignancy—chorionepithelioma, sarcoma, adeno-



acanthoma, and carcinoma of the endometrium. Benign uterine conditions requiring hysterectomy are fibromyoma, adenomyosis, fibrosis, hypertrophy, and functional bleeding not controlled by other means.

Hysterectomy is one treatment of choice when an otherwise normal uterus is associated with prolapse or procidentia, cystoectocoele and enterocele. In this connection, it may be stated that the age of the patient is no barrier to the performance of hysterectomy. It should be noted also that hysterectomy is not the only answer or even the essential part of the treatment of uterine prolapse. Neither hysterectomy nor any other single operation is a satisfactory procedure for all patients. The relief of such birth injuries should be individualized and other procedures considered and used when indicated. These include simple plastic reconstruction of the birth canal, the Manchester operation, colpocleisis, and other procedures. However, hysterectomy has many advantages. These include removal of the sagging uterus and better access to the supporting structures. The uterosacral ligaments, the cervical ligaments, and the fascial planes are more available and lend themselves to better reconstruction when the uterus is out of the way.

There are few cervical indications for hysterectomy. These include carcinoma in situ, cervical stricture and pyometra, and occasionally persisting carcinoma of the cervix following complete irradiation.

Hysterectomy of any type, and in association with any other form of treatment or procedure, is not accepted as the treatment of choice for carcinoma of the cervix. The consensus of the major gynecologic clinics of this country is that irradiation offers the best form of treatment for cervical carcinoma in any or all of its stages. The five- or ten-year results, the immediate and remote mortality, and the general well-being of the patient are all at their best when irradiation is the treatment used. Carcinoma of the cervix is not a surgical disease.

Hysterectomy is part of the treatment for tubal and ovarian malignancy, for the functioning ovarian tumors which are actually or potentially malignant, for persistent pelvic inflammatory disease with excessive uterine bleeding, and occasionally for the relief of endometriosis. Hysterectomy should be performed whenever adnexal pathology requires the removal of both tubes and ovaries. There is no clinical value in allowing the useless and potentially dangerous organ to remain when bilateral salpingo-oophorectomy is necessary.

Cesarean hysterectomy is indicated occasionally for fibromyoma, for Couvelaire uterus, or for uncontrollable hemorrhage following delivery. Cesarean hysterectomy should not be done for the purpose of sterilization nor as a means of combating obstetric infection.

The available types of hysterectomy were, and still are, subtotal abdominal hysterectomy, also called supravaginal or supracervical, total abdominal hysterectomy, and vaginal hysterectomy. Subtotal hysterectomy, particularly for uterine fibroids, held the limelight in our literature and in the operating room for many years. Endless refinements of technique became the basis for an ever-continuing series of articles. It was felt that the integrity of the cer-

vix must be maintained in order to prevent ensuing prolapse of the vagina and the further development of cystocele. In fact, the cervix was described as "the keystone of the pelvic arch," and for many years it was considered that pelvic support must, of necessity, be inadequate if the cervix were removed.

There was constant debate and controversy regarding the treatment of the cervical stump, the closure of the gaping cervical canal, the disposition of the bladder with its detached peritoneal flap, the fate of the disconnected and flapping adnexa, and the disposition of the round ligaments and lateral sacral ligament stump. Bleeding from the cervical stump, stump exudates, and the subsequent development of cervical stump infection or cervical stump carcinoma gradually led to the adoption of total abdominal hysterectomy.

The continuing practice of office gynecology gave the trained gynecologist ample opportunity for judging the merits of total versus subtotal hysterectomy. For in the gynecologist's office were seen the sequelae of subtotal abdominal hysterectomy. The frequency with which erosion, infection, polyp, bleeding, and carcinoma developed called the attention of the specialist to the disadvantages of the cervical stump. These conditions led to the production of pelvic pain, dyspareunia, dysuria, frequency of urination, and discharge as persistent or recurrent symptoms requiring treatment. Too often this meant surgical excision of the cervical stump, thus necessitating a second operative procedure. It cannot be emphasized too strongly that a subtotal hysterectomy obligates the gynecologist to continuing follow-up studies and examinations for the previously mentioned conditions and for the early detection of carcinoma of the cervical stump.

It was during those years when subtotal hysterectomy achieved its greatest popularity that the magic of irradiation therapy entered the lists. Its proponents promptly discarded all types of hysterectomy. The original indications were castration for the presence of slow-growing fibroids, various types of uterine bleeding, and, eventually, malignancy. Before long, radium appeared and became available immediately by direct application and eventually in the form of a radium bomb.

These nonoperative procedures achieved a large following almost at once. They were relatively cheap and simple, with practically no resultant mortality. The procedure required no great surgical skill. It could be carried out, therefore, not only by those gynecologists who believed firmly in the efficacy of irradiation therapy for benign conditions of the uterus but also was seized upon by the less competent and those both unwilling or unable to perform hysterectomy. It required years of failure, disappointments, and irradiation injuries to both bowel and urinary tract to relegate irradiation to the very minor and secondary role to which it is entitled.

Meanwhile, gynecologists both here and abroad were experimenting with two other types of hysterectomy, each with its own advantages. These were total abdominal hysterectomy and vaginal hysterectomy. Both of these removed the cervix as well as the corpus uteri and thus eliminated the cervix as a source of further trouble. Major pelvic surgery itself became increas-

ingly safe with continuing decreased mortality and morbidity. This change was due in part to improved anesthesia, the increased availability of blood replacement and transfusion, and the development of both chemotherapy and antibiotics.

There remained one final hurdle for the establishment of total abdominal hysterectomy and vaginal hysterectomy—the intimate anatomical relationship between the genital and urinary systems. For the trained gynecologist, it became only a matter of learning those techniques which could safely include the removal of the cervix during abdominal hysterectomy. This technique was developed by anatomic studies, by the use of bladder instillations of methylene blue and other dyes, and by the use of preliminary preoperative ureteral catheterization. Eventually, these techniques were mastered, and in the last fifteen years total abdominal hysterectomy has displaced the subtotal operation almost completely in the leading gynecologic clinics.

It has been stated on occasion that the "occasional" operator should perform subtotal hysterectomy and the trained gynecologist should perform total hysterectomy. The myth of the "occasional" operator should be exploded. The man who is qualified to perform a subtotal hysterectomy can easily qualify himself, by training and experience, to perform total abdominal hysterectomy. The man who cannot master total abdominal hysterectomy is not qualified to perform subtotal abdominal hysterectomy either. It is obvious that every man who does major gynecologic surgery must know how and when to do the proper procedure. The only indications that remain for subtotal abdominal hysterectomy are marked obesity and inaccessibility of the cervix due to either fixation or adhesions, or both.

The alternative procedure to total abdominal hysterectomy is vaginal hysterectomy. This procedure has had a slower acceptance but is gradually coming into its own proper place. Vaginal hysterectomy is chosen by the well-trained and experienced gynecologist for those patients who require vaginal reconstruction when the tumor mass is not of a size to require morcellation, when there is no malignancy, and provided there is no uterine fixation from previous pelvic surgery, pelvic inflammatory disease, or endometriosis. The advantages of vaginal hysterectomy include (1) no abdominal incision and incisional pain, hernia, or dehiscence, (2) no bowel manipulation and, therefore, less postoperative shock, ileus, or peritonitis, (3) ease of approach for the obese patient, (4) the opportunity to carry out reconstructive surgery of the vagina, bladder, and rectum as a single operative procedure.

The disadvantages of the vaginal approach for hysterectomy include inability to carry out abdominal exploration and the fact that on occasion the adnexa may be inaccessible. Furthermore, it must be pointed out that there is always the small and continuing risk of the finding of a previously undetected and unsuspected adnexal or uterine malignancy at the time of surgery. For these latter, the abdominal approach is obviously the one of choice.

Abdominal hysterectomy follows upon a wide variety of obstetrical indications. These include uncontrollable uterine hemorrhage following delivery, perforations of the uterus, spontaneous rupture of the lower uterine seg-

ment during labor, or uterine rupture following attempts at delivery, and rupture of uterine scars from previous cesarean section. Hemorrhage and infection no longer lead to obstetric mortality but the chance of survival of the patient is dependent directly upon the speed of recognition. It must be emphasized that the need for sterilization of the patient is never, per se, an indication for hysterectomy.

The comparative frequency of vaginal hysterectomy, total abdominal hysterectomy, and supracervical hysterectomy varies from hospital to hospital. As previously stated, the majority of the major gynecological clinics in this country report an incidence of 5 per cent or less for incomplete abdominal hysterectomy. In some institutions, the overwhelming majority of the hysterectomies performed are total abdominal with very few or no vaginal hysterectomies being done except for procidentia. A few departments show what might be termed an overenthusiasm for vaginal hysterectomy and as a consequence 80 to 90 per cent of all hysterectomies done in these clinics are vaginal hysterectomies.

A happy middle ground has been found in those institutions in which an attempt is made to follow the indications and contraindications as previously outlined and where enthusiasm for one type or the other is not allowed to run rampant. A study of their statistics indicates that the more ideal incidence which they achieve for the various approaches is as follows: total abdominal hysterectomy, 50 to 60 per cent, vaginal hysterectomy, 35 to 45 per cent, and subtotal abdominal hysterectomy, 5 per cent or less. It seems obvious that the best results for all concerned are achieved only by strict adherence to the indications and contraindications for each type of hysterectomy and to the continuing individualization of each patient for whom hysterectomy is indicated.



## RESULTS OF VAGINAL HYSTERECTOMY; IMMEDIATELY AND TWO AND ONE-HALF TO SEVEN YEARS AFTER OPERATION

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SEVERAL reports concerning the indications, techniques, and immediate results of vaginal hysterectomy are found in the medical literature. The long-term anatomical and functional results of this operation have not received proportionate attention.<sup>1-3</sup> This information is of first importance in determining both the indications for the procedure and in evaluating our present techniques. It is also important to distinguish between results in operations done primarily for uterine prolapse and those done for such conditions as myomas, persistent menorrhagia, and other diseases of the uterus not associated with prolapse.

We have reviewed the 163 consecutive vaginal hysterectomies performed at the Colorado General Hospital and Denver General Hospital from July, 1946, to July, 1951. We have been able to follow 71 of these patients in our own clinic for a minimum time of two and one-half years to a maximum of seven years. Each of the 71 patients has been examined within the past six months. Two additional patients have been followed by their own private physicians who filled out questionnaires covering the points mentioned in this paper. One other patient did not return to clinic but reported on a form sent to her. This is a total of 74 cases on which we have all the necessary information. In 32 instances, the operation was performed by staff physicians. The remaining 131 have been done by the resident staff under supervision of staff physicians. As senior residents became more proficient, the staff physician was not always present for the operation though he had examined the patient prior to surgery.

### Clinical Material

There were 31 patients with first-degree uterine prolapse; i.e., the cervix descended but remained within the vaginal orifice. In 71 individuals, the prolapse was second degree; i.e., the cervix was at or near the introitus. Twenty-three patients were classified as having a third-degree uterine prolapse with the entire uterus and vagina protruding from the introitus. In 38 cases, other reasons were the prime indication for surgery as listed in Table I.

The patients with menorrhagia, chronic cervicitis, and myomas also had cystoceles or rectoceles that required repair. One patient with carcinoma of the cervix was treated by the radical Schauta-type vaginal hysterectomy because

of associated complete uterine prolapse. The other cervical carcinoma was diagnosed preoperatively as carcinoma in situ but serial sections of the cervical lesion revealed it to be early invasive epidermoid carcinoma. A marked cystocele and rectocele were the reasons for choosing the vaginal operation for this patient. The adenocarcinoma of the fundus was in a 74-year-old woman and vaginal hysterectomy was considered safer than the abdominal operation in view of an accompanying second-degree prolapse. The average age of patients operated upon was 46 years. The youngest patient was 26, while the oldest was 74.

TABLE I. INDICATIONS FOR VAGINAL HYSTERECTOMY

PRIMARY SURGICAL INDICATION		SECONDARY SURGICAL INDICATION	
Uterine prolapse, first degree	31	Uterine prolapse, first degree	5
Uterine prolapse, second degree	71	Uterine prolapse, second degree	1
Uterine prolapse, third degree	23	Uterine prolapse, third degree	1
Menorrhagia	13		
Myomas	8		
Cervicitis	4		
Cancer of cervix	4		
Cystocele and rectocele	3		
Sterilization with rectocele and cystocele	2		
Pyometra	2		
Third-degree perineal tear	1		
Dysmenorrhea	1		
Total	163		7

*Other Procedures.—*

Procedures performed coincident to vaginal hysterectomy are listed in Table II.

TABLE II. ADDITIONAL PROCEDURES

OPERATION	NO.
Anterior and posterior colporrhaphy	147
Dilatation and curettage	10
Anterior colporrhaphy	5
Repair of third-degree perineal laceration	3
Oophorectomy	3
Salpingo-oophorectomy	2
Posterior colporrhaphy	1
Colpectomy	1

**Operative Method**

The patient was usually in the hospital 24 hours before operation. The preparation of the perineum and vagina was done in the operating room, using soap, water, and a mild antiseptic solution. The hair had previously been removed from the vulval area. Cyclopropane combined with ether was the most frequently chosen anesthetic agent. Local anesthesia supplemented by intravenous Pentothal Sodium was used for a few operations. Spinal anesthesia was rarely used.

*Operative Technique.—*

An inverted T incision of the anterior vaginal wall is made, extending from the cervix to the urethral meatus. The pubocervical fascia is dissected free from the vaginal epithelium. The insertions of the pubocervical ligaments are clamped, cut, and tied on either side. The urinary bladder is advanced and

separated from the uterus. The peritoneum of the anterior cul-de-sac is entered. The vaginal tissue surrounding the cervix is then circumcised and the posterior cul-de-sac peritoneum is entered. The uterosacral ligaments and the cardinal ligament attachments to the uterus are then clamped, cut, and tied with No. 0 chromic catgut. The uterine vessels are identified and separately ligated. The adnexal attachments to the uterus and the round ligaments are then clamped, cut, and tied, and the uterus is removed. The ovaries are inspected but are not removed if normal. The cul-de-sac of Douglas is examined for an enterocele. If an enterocele is found, it is removed, and the uterosacral ligaments are approximated in the midline with interrupted sutures.

The pelvic peritoneum is closed with a running suture. The round ligaments and the adnexa are permitted to retract laterally and are not sutured together in the midline.

The uterosacral ligaments are approximated in the midline. If a severe degree of uterine prolapse had been present the elongated uterosacral ligaments are sutured to the anterior pubic rami as far anteriorly as possible. The two cardinal ligaments are then approximated and, in turn, are joined to the uterosacral ligaments. The previous cervical attachments of the pubocervical fascia are attached to the cardinal ligaments and the uterosacral ligaments. All these structures are then joined to each other at the apex of the vagina. Frequently the major ligamentous structures are joined by a continuous Heaney-type suture.<sup>4</sup>

The anterior vaginal wall is plicated by suturing the pubocervical fascia together in the midline with interrupted chromic No. 0 catgut. The pubocervical fascia is repaired from below upward until the urethra is reached. The urethra and vesical neck are supported by the pubocervical fascia. Two to three Kelly urethrocele plication sutures of the periurethral tissue are added. The epithelium of the anterior vaginal wall and the vaginal apex is closed. No drain is placed in the vaginal apex or in the cul-de-sac of Douglas.

The operation is completed by a repair of the posterior vaginal wall, the extent of which is dictated by the degree of relaxation.

The vagina is then packed snugly with a gauze strip which is removed 24 hours later. This is for the purpose of ensuring hemostasis and for preventing the formation of a subvaginal hematoma. An indwelling catheter is placed in the bladder and remains there until the fifth or sixth postoperative day. Most patients receive a 500 c.c. blood transfusion during the operation.

#### *Postoperative Care.*—

The patients are permitted to be out of bed the day following operation. The catheter may be clamped closed for periods while the patient is out of bed. One of the sulfonamide urinary antibiotics is prescribed to reduce the incidence of postoperative urinary tract infections. A sulfonamide cream is inserted into the vagina daily for two weeks, starting one week after operation.

### **Results**

#### *Postoperative Morbidity.*—

The average length of hospital stay was ten days, which compares quite favorably with Edwards's<sup>5</sup> reported 14 days and Brill's<sup>6</sup> 11 days. Morbidity

of the total group was 34.9 per cent. We accepted the standard definition of morbidity, i.e., a temperature of 100.4° F. for two or more days after the first 24 hours following surgery. Brill reported a morbidity of 31.9 per cent and Leventhal<sup>7</sup> reported 39.3 per cent postoperative morbidity. Both of these papers appeared in 1951 and cover approximately the same years as our cases. Turner<sup>8</sup> reports a morbidity of 7 per cent with the use of penicillin vaginal suppositories preoperatively, a considerable improvement. We did not use such suppositories nor did we use antibiotics postoperatively unless there was a specific indication.

#### *Operative Mortality.—*

One patient died on the seventeenth postoperative day of bronchopneumonia. She was 59 years old and was operated on for complete uterine prolapse. Severe hypertensive cardiovascular disease was a contributing factor to her death. Our mortality rate was 0.6 per cent for the 163 vaginal hysterectomies, which is higher than Weaver's<sup>9</sup> rate of 0.31 per cent in 13,939 vaginal hysterectomies collected from the literature. Rhoads<sup>10</sup> reported a mortality rate of 1.04 per cent in 205 similar operations.

#### *Postoperative Complications.—*

The list of postoperative complications in the 163 vaginal hysterectomies (Table III) is of interest and follows the same pattern as those in other reports,<sup>5</sup> with urinary tract infections the most frequent complication.

TABLE III. POSTOPERATIVE COMPLICATIONS

COMPLICATION	NO. OF CASES
Urinary retention	19
Cystitis	11
Pyelitis	8
Shock, during operation or immediately postoperative	7
Pneumonia	3
Abscess in vaginal vault	2
Abscess in perineum	1
Atelectasis	1
Hematoma, anterior vaginal wall	1
Peritonitis	1
Rectovaginal fistula	1

The shock was in all cases quickly corrected by blood transfusion. The rectovaginal fistula developed in the case of the Schauta operation for carcinoma of the cervix where a colpectomy was done. It was corrected a few months postoperatively. It is significant that thromboembolic disease and urinary fistulas did not complicate any of the 163 vaginal hysterectomy operations. During two operations the bladder was inadvertently opened but repair was done at once without further complication. A number of patients had difficulty voiding following removal of the catheter postoperatively. Nineteen patients required reinsertion of the indwelling catheter or had persistent urinary retention for more than one or two days following removal of the catheter. All patients were eventually able to void normally and were not discharged until the residual of urine was less than 50 c.c. The longest duration of postoperative urinary retention was 17 days.



*Results of Examinations Done Two and One-Half to Seven Years After Operation.—*

Seventy-four patients were available for study of the late results of vaginal hysterectomy. Seventy-three of them were examined within the past six months and the minimum period since operation was two and one-half years. The anatomical results were considered excellent with no descent of the vault, well-supported anterior and posterior vaginal walls, and a good functional length of the vagina in 57 patients. Thus the end results were completely satisfactory in 77 per cent of our vaginal hysterectomies. Eleven others (14.7 per cent) did not have perfect anatomical results but had no symptoms. Six patients had incomplete relief of symptoms following surgery and 4 of these patients were reoperated upon. Table IV gives the details of the imperfect anatomical results, as well as whether the indication for the surgery was prolapse.

TABLE IV. UNSATISFACTORY RESULTS

DEFECT	INDICATION			
	PROLAPSE			OTHER
	1°	2°	3°	
<i>Asymptomatic.—</i>				
Enterocele	1	1	1	
Cystocele	1	3		1
Deficient perineal body				1
Shortening of vagina		1		1
<i>Symptomatic.—</i>				
Prolapse of vault		1		
Enterocele		1		
Cystocele with stress incontinence	1	1		1
Rectocele	1			

In one patient there was complete prolapse of the vagina six months following surgery. Four more patients were found to have a postoperative enterocele, an incidence of 5.3 per cent. Of the 11 patients without entirely satisfactory anatomical results, none developed symptoms that warranted further attempts at surgical repair. The cystoceles, for instance, were merely mild relaxations of the anterior vaginal wall. The two patients with shortening of the vagina were both 60 years of age and had no complaints referable to this finding. Of 36 patients who had stress incontinence before operation, 3 had recurrence of this symptom after vaginal hysterectomy with repair of the vesical neck defect, a recurrence rate of 8.3 per cent. Our vaginal hysterectomy results are summarized in Table V.

TABLE V. RESULTS OF VAGINAL HYSTERECTOMY; TWO AND ONE-HALF TO SEVEN YEARS AFTER OPERATION

	NO. CASES	PERCENTAGE
Entirely satisfactory	57	77.0
Anatomically less than satisfactory	17	23.0
Anatomically unsatisfactory but asymptomatic	11	14.6
Anatomically unsatisfactory and symptomatic following surgery	6	8.1
Postoperative enterocele	4	5.3
Prolapse of vaginal vault	1	1.4
Recurrent stress incontinence	3	8.3

*Influence of the Absence or Presence of Uterine Prolapse Before Operation on Final Results.—*

The results in the 74 cases followed two and one-half years or longer are divided into the patients who had preoperative prolapse and those that did not. Others<sup>2, 10, 11</sup> do not state in reporting results the number of cases in which prolapse was present. The end results might be expected to be different when the operation is done for uterine prolapse, as compared to a series of vaginal hysterectomies performed on patients with good uterine and vaginal supporting structures. In 58 of our 74 patients followed, some degree of uterine prolapse was present before operation. It was the primary indication for surgery in 54 patients while in 4 others uterine descensus was present along with more serious uterine disease. Division as to the degree of prolapse shows 15 cases of first-degree, 35 cases of second-degree, and 8 cases of third-degree uterine prolapse. Of the 6 symptomatic failures, 5 followed surgery for prolapse. One failure occurred in a patient not operated on for uterine prolapse. The more serious anatomical defects such as descensus of the vaginal vault and enterocele were found among the patients operated on for prolapse.

All the patients followed were questioned concerning dyspareunia after vaginal hysterectomy. Five patients (6.7 per cent) had this complaint. In 2 of these patients, enteroceles were present, while, in the other 3, the anatomical results of the operation were entirely satisfactory. This may be compared with an incidence of 9.9 per cent dyspareunia in Te Linde's<sup>12</sup> cases of the Spaulding-Richardson composite operation. Other literature reviewed on vaginal hysterectomies was not specific on this point.

**Comments**

Comparison of our results with Everett's<sup>1</sup> early report gives a more favorable picture of the vaginal hysterectomy operation than he presented. He found only 47 per cent of his cases entirely satisfactory as compared to our 77 per cent. Twenty-nine per cent of his were unsatisfactory both anatomically and symptomatically as compared to 8.4 per cent in our series. Emmert<sup>2</sup> and Danforth<sup>3</sup> have reported satisfactory results of 87.33 per cent and 87.5 per cent, respectively. These authors do not mention the number of unsatisfactory anatomical results that have symptomatic relief. From the viewpoint of symptomatic relief our operation is 92 per cent successful.

The more serious anatomical failures were in the prolapse group. An encouraging finding has been the excellent support of the vaginal vault with only one case of prolapse of the vagina. A frequent criticism<sup>12</sup> of this operation has been that it does not leave sufficient support for the vaginal vault. Our own experience has been that vaginal hysterectomy, if accompanied by the proper plastic repair of vaginal supports, is an excellent operation for the cure of uterine prolapse, and is not complicated by later vaginal vault prolapse except in a rare instance. We wish to emphasize that the removal of a prolapsed uterus with failure properly to repair vaginal supporting structures is, however, an inadequate and a very poor method for surgically treating uterine prolapse. It is likely that a portion of the enteroceles went unrecognized at

operation and were not properly repaired. A favorable finding is the low incidence of unsatisfactory results in 8 patients with third-degree uterine prolapse. Only one developed an anatomical defect, an enterocele. This patient previously had had a Manchester-Fothergill operation for uterine prolapse and the prolapse had recurred.

Careful surgical attention to the cure and prevention of stress incontinence has been emphasized in the practice and teaching of all our vaginal plastic work. There were only 3 patients who had recurrent stress incontinence. Of 36 patients who presented this complaint before surgery, 33, or 92 per cent, were cured when examined two and one-half to seven years after surgery. Even though stress incontinence is not present before operation, the pubocervical fascia is sutured beneath the bladder and its neck, and the periurethral tissues are plicated. By establishing this as an adjunct procedure to vaginal hysterectomy, the cure and prevention rate of stress incontinence has been excellent.

Much has been written and spoken about the desirability of removing ovaries from women at or near the age of the menopause, when such a patient undergoes abdominal hysterectomy. We have never been impressed with the arguments for removal of normal ovaries at any age. In 5 patients among 163, unilateral oophorectomy was performed in conjunction with vaginal hysterectomy. Experience has taught us the folly of removing ovaries when vaginal plastic operations are done. The senile contractions of genital tissues that ensue are enough to negate an otherwise excellently performed vaginal plastic operation. We, therefore, inspect but never remove normal ovaries when vaginal hysterectomy is done. Our policy is the same when the uterus is removed abdominally.

Two aspects of vaginal hysterectomy remain to be solved: blood loss and urinary retention. In 88 of the 163 operations, blood transfusion was required. We are working on methods to reduce the blood loss that is characteristic of the operation in our hands. Our second problem is that of postoperative urinary retention. We have tried every drug and method to remove this minor but annoying postoperative complication. It is our impression that the best permanent relief of stress incontinence and cystocele symptoms occurs among the group who have difficulty in voiding after surgery. We believe that the extensive dissection of the pubocervical fascia from the bladder and the edema of suture lines cause the patient's inability to void until a delayed date. Any method that will help us avoid the postoperative retention of urine after vaginal hysterectomy accompanied by vaginal plastic procedures will be a welcome addition to our practice.

### Conclusions

1. Vaginal hysterectomy is an excellent operation for the cure of uterine prolapse, if proper repair of the vaginal and urinary bladder supporting structures is performed coincidentally.

2. Vaginal hysterectomy is a valuable and a safe procedure to be used in conditions other than uterine prolapse if the uterus is not overly enlarged or fixed in the pelvis.

3. Prolapse of the vaginal vault is a rare complication of vaginal hysterectomy in our clinic.

4. Surgical cure or surgical prevention of stress incontinence should be a part of each vaginal hysterectomy procedure done in the presence of relaxation.

5. Surgical methods should be developed to minimize blood loss associated with vaginal hysterectomy accompanied by vaginal plastic operations.

6. Postoperative urinary retention remains a vexing clinical problem.

### Summary

1. One hundred sixty-three vaginal hysterectomy operations were performed at Colorado General Hospital and Denver General Hospital from July, 1946, to July, 1951.

2. Our technique for vaginal hysterectomy is briefly presented.

3. Seventy-four of the 163 patients have been followed for periods varying from two and one-half to seven years.

4. Seventy-seven per cent of results were entirely satisfactory; 14.6 per cent were less than satisfactory anatomically but were asymptomatic, and 8.4 per cent were anatomically unsatisfactory and symptomatic.

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## LOWER URINARY TRACT FISTULAS IN WOMEN

### A Study Based on 292 Cases

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EVERY man born into this world affects in some manner the lives of those about him. For many the sphere of influence is limited. Others make their presence felt far beyond community or national borders. Dr. George Kosmak belongs to the latter group. As long-time Editor of this JOURNAL, he has helped mold contemporary thought and practice in the field of obstetrics and gynecology. His wisdom and keen editorial judgment have contributed significantly to the present high standard of obstetric and gynecologic care.

While there is a wide variety of injuries which can and do affect the lower urinary tract in women, we shall limit this discussion to those which cause fistula formation. By so doing we intend no belittlement of the equally important and all too common incontinence which occurs in an intact urinary tract. Indeed, we consider stress incontinence today more important than fistulas. Not only is stress incontinence more common but it is still inadequately explained and its treatment far from satisfactorily crystallized.

Fistula formation between the lower urinary tract and vagina has long been associated with neglected and difficult childbirth. Today, American obstetrics accounts for few injuries of this nature, a reflection of the tremendous improvement which has occurred in obstetric practice in this country.

Excessively long labor leading to prolonged pressure and avascular necrosis of the base of the bladder and difficult or forced birth resulting in rupture and tearing were once the principal causes of fistulas. While birth trauma is still an important etiological factor in some parts of the world, its causative role in fistula formation is today relatively unimportant in the United States. Obstetric trauma was a responsible factor in only 43, or 14.7 per cent (Table I), of the 292 cases in our series. Fistulas resulting from birth injuries occurred in the bladder or urethra or both and were generally larger than those resulting from surgical trauma. The greater extent of the injury in postpartum cases did not, however, imply increased difficulty in correction. As a matter of fact, many fistulas resulting from birth injury were, generally speaking, easier to close because of their ready accessibility. The uterus was invariably present and traction on the cervix in parous individuals permitted good exposure and thus facilitated closure.

Factors contributing to a reduction in postobstetric fistulas include:

1. Improved prenatal care, especially better evaluation of cephalopelvic disproportion before or early in labor.

2. Freer use of elective cesarean section for marked cephalopelvic disproportion.

3. Reduction in the number of traumatic deliveries as a result of: (a) better understanding of the mechanism of labor; (b) fewer forced labors through reduction in the use of unindicated, poorly timed, and excessive ecbolies during labor; (c) discontinuance of floating and high forceps operations and of unindicated version and extraction; (d) wider recognition of the traumatic consequences of delivery through the incompletely dilated cervix.

Widespread observance of these and other principles of good obstetric care have practically eliminated the risk of fistula formation except in the now relatively uncommon, badly neglected case.

Of intermediate importance in the production of urinary fistulas, in our series, was carcinoma of the cervix and vagina. Cancer was responsible for 100, or 34.2 per cent (Table I), of the 292 fistulas seen by us. In most instances the fistula occurred subsequent to neoplastic invasion of the base of the bladder. Because the fistula and associated incontinence often appeared after the administration of irradiation therapy, many afflicted patients were inclined to blame the treatment rather than the neoplasm for the fistula. While improper dosage and/or application of irradiation therapy may cause tissue damage leading to fistula formation, in the majority of these individuals the carcinoma was far advanced and responsible for extensive destruction of the base of the bladder. In many instances fistula formation had already occurred prior to irradiation while in others destruction of the neoplasm by means of irradiation led to avascular necrosis, secondary tissue loss, and fistula formation.

TABLE I. PRIMARY CAUSE, 292 URINARY TRACT FISTULAS IN FEMALE

CAUSE	NUMBER	PERCENTAGE
Pelvic surgery	132	45.2
Pelvic carcinoma	100	34.2
Birth trauma	43	14.7
Other causes	17	5.8
Total	292	99.9

Most patients in this category were admitted to our service with urinary incontinence as their main complaint. So long as there continue to be advanced cases of pelvic malignancy we shall continue to see urinary fistulas of neoplastic origin. Fortunately, considerable help can be given to some of these unfortunate individuals. Despite the continued presence of carcinoma, the fistula may sometimes be closed and the patient's discomfort reduced by making her dry (Fig. 1).

Most important among the several causes of fistula formation in the lower urinary tract in our series was trauma sustained at the time of pelvic surgery. Thus, 132, or 45.2 per cent of the patients in our series, developed their fistulas subsequent to pelvic surgery (Table I). As shown in Tables II and III, in 97, or 73 per cent, hysterectomy of one kind or another had preceded the fistula formation. Vaginal operations other than hysterectomy contributed to another 18.9 per cent; the remaining 7.5 per cent appeared following other pelvic opera-

TABLE II. TYPE OF OPERATION WHICH PRECEDED FISTULA

TYPE	NUMBER FISTULAS	PERCENTAGE
Hysterectomy	97	73.4
Anterior colporrhaphy	17	12.9
Cervix operation	6	4.5
Excision of diverticula	2	1.5
Other	10	7.5
Total	132	99.8

TABLE III. TYPE OF FISTULA WHICH FOLLOWED HYSTERECTOMY

OPERATION	VESICOVAGINAL	URETHROVAGINAL	URETEROVAGINAL
Subtotal hysterectomy	0	0	2
Total abdominal hysterectomy	54	3	8
Vaginal hysterectomy	18	3	1
Radical hysterectomy	3	0	5
Total	75	6	16

TABLE IV. CLASSIFICATION ACCORDING TO TYPE, 292 URINARY TRACT FISTULAS

TYPE	NUMBER	PERCENTAGE
Vesicovaginal	235	80.4
Urethrovaginal	36	12.3
Ureterovaginal	21	7.1
Total	292	99.8

tions. The location or type of fistula encountered by us is shown in Table IV and, as was to be expected, the vast majority were of the vesicovaginal variety.

Because pelvic surgery is today the major cause of urinary fistulas in women it is desirable to consider the question of why this is so. Doubtless unrecognized direct injury to the bladder occurring at the time of operation plays an etiological role (Fig. 2). In this category we may include such things as incision into or actual tearing of the bladder, incision of the ureter, and similar trauma. Uncontrolled leakage of urine commencing shortly after operation strongly suggests such operative accidents to the lower urinary tract. While accidental injury to the bladder occasionally occurs at the time of pelvic surgery it is usually recognized and promptly repaired without residual symptoms. Unrecognized injuries are not common but probably occur during bladder mobilization or as a consequence of excessive force applied through improper or sharp bladder retraction.

The late appearance of uncontrolled urinary leakage—days or even weeks after operation—suggests a different causative factor. In these late post-operative (or postpartum) instances of uncontrolled urinary leakage, it appears that avascular necrosis plays an important role. This may occur secondary to the placement of suture material in the bladder or follow prolonged retractor pressure, leading to trauma and subsequent necrosis of the affected area. Possibly we do not guard against this sort of injury as carefully as we should.

In somewhat the same category are those injuries to the ureter caused by clamping or ligation. Unrecognized ligation of both ureters at the time of pelvic operation must be rare. Presumably such an accident would be recognized and undone within a day or two after operation. Damage to a single ureter occurs more often and accounts for the ureterovaginal fistulas occasionally seen. Seri-

ous interference with the blood supply to the ureter may occur as a consequence of extensive dissection and freeing of the ureter from its vascular bed during radical dissection of the pelvis (Fig. 3). With increasing experience one may question the desirability of and need for such procedure. While there are lymph vessels all along the ureter, few important nodes are to be found except at its lower pelvic portion.

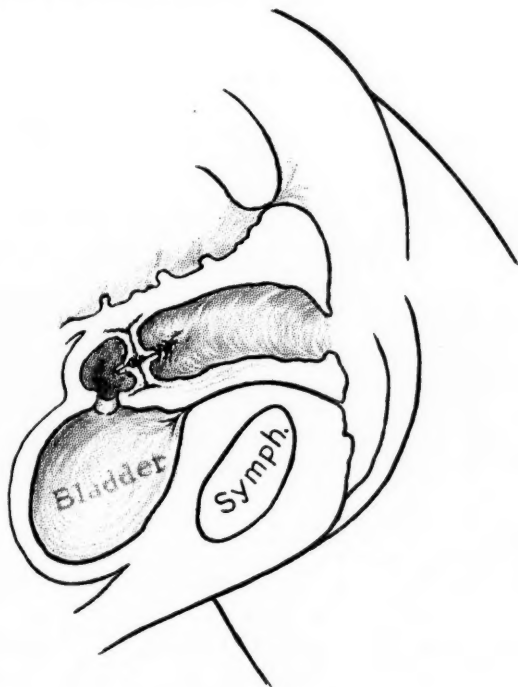


Fig. 1.

Fig. 1.—Because of scarring and devascularization subsequent to irradiation treatment, patients with bladder or rectal fistulas located high in the vagina may not be suitable for repair by ordinary methods. For these patients closure of the vagina below the fistula site at a level where healthy tissue may be utilized, as illustrated, often serves to render the patient continent.



Fig. 2.

Fig. 2.—The finger points to a vulnerable area in the downward displacement of the bladder at the time of hysterectomy. Mobilization of the bladder may be accomplished by either sharp or blunt dissection. In either instance caution should be exercised in order to avoid bladder trauma. Caution must also be observed to avoid catching the bladder when suturing the vaginal cuff.

One contributory factor in the causation of avascular necrosis which appears to be overlooked and underestimated in importance is the superfluous use of and excessive tension placed upon suture material used in repairing a cystocele. A number of the 17 fistulas which followed cystocele repair and anterior colporrhaphy in our series appeared to have been on this basis. The abundant vascularity of this area plus the occasional difficulty encountered in securing satisfactory hemostasis may conceivably lead to blind suturing or to the excessive use of suture material and thus serve as an additional contributory factor.

While urinary fistulas in women are decreasing in number the likelihood of their occurrence may be minimized by observing certain precautions. These may be listed as follows:



1. *In Obstetrics:* Recognize that long difficult labor and/or operative delivery can be traumatic to the bladder as well as to the birth canal. Therefore minimize trauma by:

- A. Keeping the patient's bladder empty.
- B. Recognizing cephalopelvic disproportion early. If risk of delivery per vaginam appears excessive, resort to elective cesarean section.
- C. Not attempting operative delivery without proper indication nor until all requirements have been fulfilled.
- D. Not hesitating to obtain consultation and assistance.
- E. Observing, in so far as possible, the normal mechanism of labor in carrying out delivery.
- F. Carefully inspecting the birth canal for injuries after every long, difficult, or complicated delivery.
- G. Repairing lacerations promptly and carefully.
- H. Inserting an indwelling catheter into the bladder whenever excessive trauma is suspected. Small injuries may heal spontaneously if relieved of intravesical pressure.

2. *In Gynecological Vaginoplasties:* In those involving the anterior vaginal wall the risk of bladder and urethral trauma may be minimized by:

- A. Knowing the anatomy of this area prior to operation.
- B. Using aids which minimize the hazard of trauma and/or promptly indicate presence of injury, thus: (1) use of catheters when necessary (urethral and/or ureteral); (2) use of methylene blue solution (1 per cent), 2 to 4 ounces in the bladder.
- C. Avoiding excessive size and amount of suture material.
- D. Guarding against excessive tension in the placement of sutures.
- E. Securing adequate hemostasis but avoiding blind suturing and mass ligation.

3. *In Laparotomy for Hysterectomy:* Bladder and ureteral damage may be lessened by:

- A. Securing adequate exposure.
- B. Exercising care in dissecting the bladder free from the uterus and anterior vaginal wall.
- C. Avoiding excessive force and traumatic retraction.
- D. Carefully palpating or visualizing the ureters lateral to the cervix. Avoiding excessive dissection of the ureters in radical hysterectomy.
- E. Recognizing fully the calculated risk that radical hysterectomy for cervical carcinoma unresponsive to irradiation therapy carries with it in the additional possibility of fistula formation due to devascularization already caused by irradiation.
- F. Using an indwelling catheter during the first 3 to 5 days following extensive pelvic surgery with obvious trauma to the bladder. A relaxed bladder favors primary healing of incisional or lacerated trauma.

Despite observation of all reasonable precautionary measures there will still be the occasional case. Consequently the management of these unfortunate accidents remains an important and sometimes troublesome problem. Great strides have been made since Marion Sims, Bozeman, Simon, Wützer, and others pioneered in their surgical correction. For most of the infrequent uretero-vaginal fistulas reimplantation of the lower end of the ureter into the bladder is the logical treatment. This is best accomplished through the abdomen, either

as a transperitoneal or, in some instances, as an extraperitoneal procedure. The ordinary vesicovaginal fistula, whether it be postpartum or postoperative, is no longer a menacing problem. With care and observation of certain basic principles, repair may be consistently accomplished. Some of the principles essential to satisfactory repair are worth mentioning.

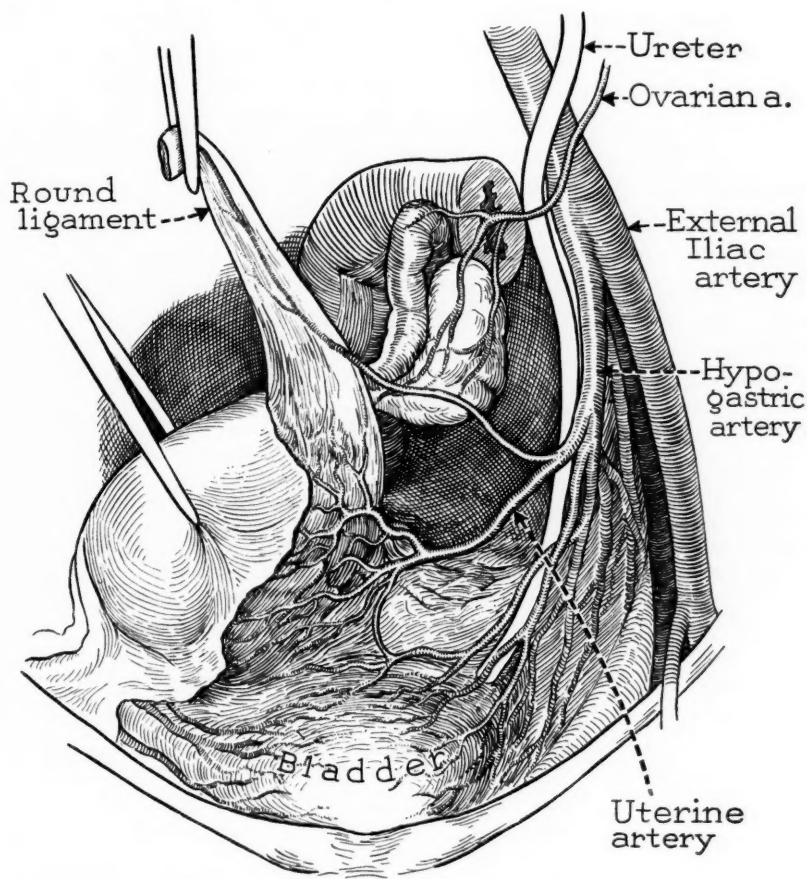


Fig. 3.—The intimate relationship between the lower portion of the ureter and the uterine vessels (veins not shown) is a factor predisposing to ureteral injury. Identification of the ureter by palpation or visualization at the time of hysterectomy helps minimize trauma to the ureter.

### Treatment of Vesicovaginal Fistulas

Once the uncontrolled escape of urine has been positively established, whether it be after delivery, pelvic surgery, or other trauma, the next step lies in determining the exact location and extent of the damage. While this always includes urologic and gynecologic evaluation, the former may, at times, be temporarily deferred. Thus, if the leakage is noted soon after operation or delivery, the patient's condition may warrant delay (unless, of course, the nature of the injury is such as to call for immediate attention). In the case of small postoperative bladder fistulas spontaneous healing is a possibility. This fortuitous outcome is aided by catheter drainage of the bladder. Healing may

occur promptly or after a period of several weeks. Should spontaneous recovery fail to take place after 12 weeks, it may be assumed that epithelization of the fistula has taken place and the likelihood of spontaneous closure is not great (although it may still occur in a few cases). Because of the persistent wetting an explanation of the situation to the patient and her family is necessary. A simple statement of fact, and an explanation of what may be expected, both as to spontaneous healing and ultimate prognosis are desirable. Patients are more cooperative and less disturbed when they understand that time is an important factor both in spontaneous recovery and in the evaluation of what may have to be done. Except when immediate repair or restoration of continuity (ureteral) is indicated, the display of undue haste in resorting to surgery often complicates the problem. This understandable urge on the part of both patient and physician to bring a stop to the leakage has, in some instances, led to premature surgery, before the tissues have fully recovered from the original trauma. Such premature attempts at closure often terminate in failure. Once it becomes apparent that spontaneous healing is not likely to occur, every precaution should be exercised toward making corrective surgery successful. To this end the following are important:

1. Complete urologic evaluation with exact localization of the fistula in relation to the urinary tract. (Is it a uretero-, a vesico-, or a urethrovaginal fistula? Where is it located in relation to the ureteral orifices, the internal bladder sphincter, and the base of the bladder?)

2. Optimum health of the patient and the structures to be repaired. Generally, several months or more are required for this purpose. During this time observance of the following preparatory measures will contribute toward better tissue health and will favor postrepair healing: (a) local cleanliness (douches); (b) an acid urine; (c) reduction of infection (use of antibiotics and urinary antiseptics); (d) improvement of the blood supply by the administration of estrogen (especially in postmenopausal women); (e) periodic inspection to determine progress, health of the tissues, and effectiveness of the measures used; (f) improvement of the patient's general health through a high-protein diet, vitamins, iron, rest, etc.

When it appears that the proper time for repair has arrived, a successful outcome may still be blocked by the nonobservance of certain principles fundamental to sound surgical repair:

1. Understand fully the location, size, and nature of the lesion to be corrected and what it is you propose to accomplish.

2. Be sure the patient has been properly prepared.

3. Obtain the best possible exposure of the area to be closed. Special positioning of the patient (Fig. 4) and efficient retractors (Fig. 5), instruments, lights, and assistance are important.

4. Achieve free mobilization of the vaginal mucosa, bladder, or urethra as required. The ease with which free mobilization is accomplished varies with the type, size, location, and the amount of scarring (previous operative attempts) present. Several procedures may be used to make mobilization easier. Thus, one may incise the vaginal mucosa around the fistula and, by means of a traction suture, pull on the bladder mucosa to facilitate dissection of the surrounding vagina. This may also facilitate approximation of the bladder muscularis (Fig. 6). Sometimes it is easier to incise the vaginal mucosa some distance from

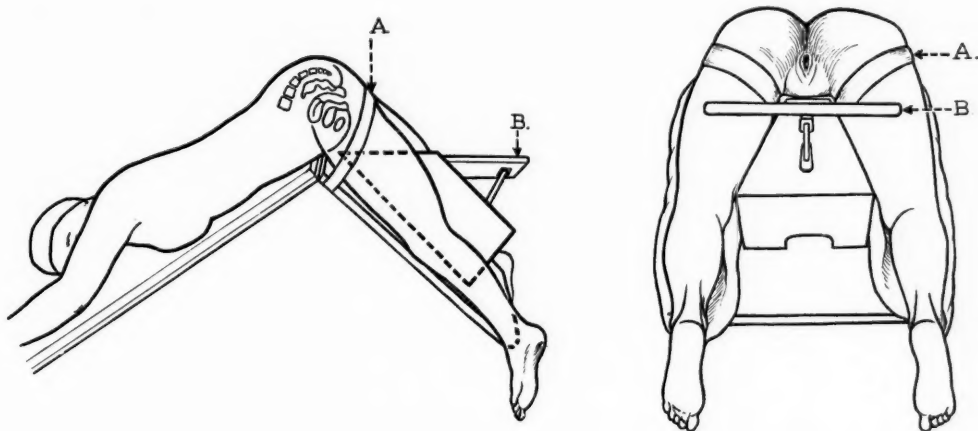


Fig. 4.—While the lithotomy position is satisfactory for the repair of the postobstetric fistulas, it does not permit good exposure of the high, posthysterectomy variety. For the latter we use the inverted Trendelenburg or jackknife position (a modification of the knee-chest position used by the pioneers in this field). The use of a "positioning unit or board," as shown (B) on the lower end of the operating table, aids in standardizing the position. Adhesive strips as shown above (A) facilitate exposure of the operative field, especially in obese patients.

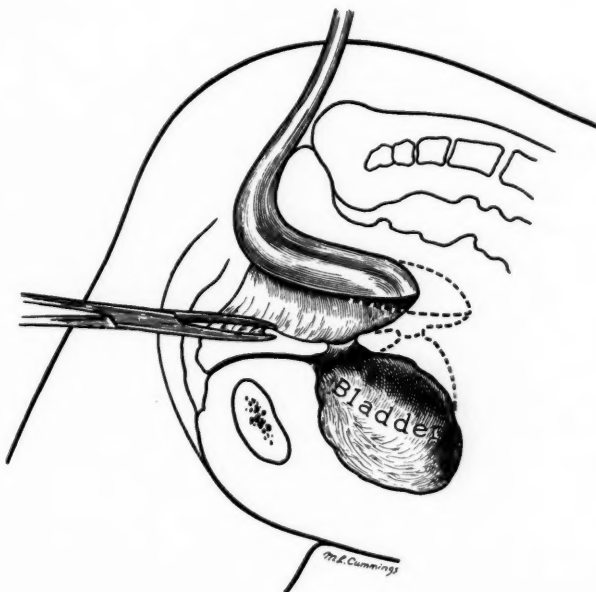


Fig. 5.—Improper use of retractors at the time of laparotomy may cause tissue injury. Improper retraction at the time of fistula repair may interfere with exposure and repair. As shown above, use of a long-bladed Sims speculum (broken line) can force the fistula higher in the vagina making it less accessible for closure. The short-bladed Sims speculum, as illustrated, permits downward traction and better exposure of the posthysterectomy bladder fistula with the patient in the inverted Trendelenburg or jackknife position.

the fistula in order to locate readily the line of cleavage between the bladder and vagina. Once this plane has been clearly established the dissection may be carried up to and around the fistula.

5. Almost any fine suture material may be used. However, nonabsorbable sutures (silk or cotton) must be removed from the vaginal mucosa and they



favor calcareous deposition when exposed in the bladder. Consequently, we prefer either No. 0000 or No. 00000 chromic catgut throughout. Avoid excessive suture material.

6. Approximate raw surfaces in a layer-for-layer manner, and without tension.

7. Remember, Nature heals—not the surgeon. We can only bring tissues together so as to facilitate healing; therefore, avoid strangulation, merely approximate the layers in the direction of least tension.

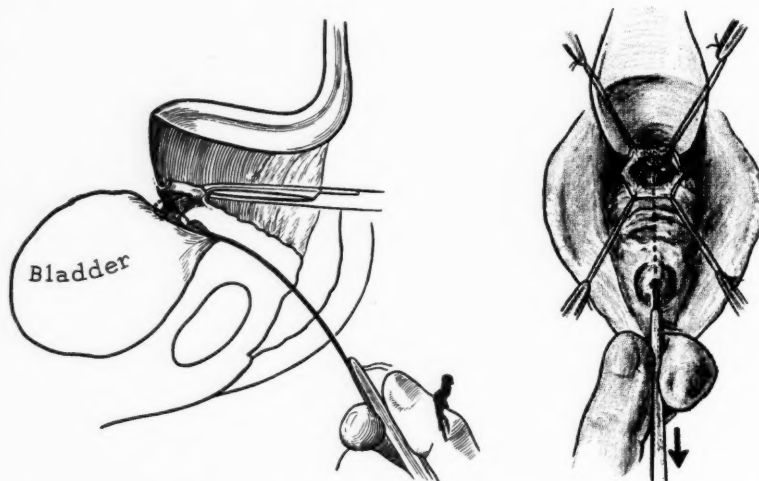


Fig. 6.—The use of traction sutures will occasionally facilitate mobilization and closure of vesicovaginal fistulas.

Proper aftercare is likewise important. In our experience the following steps have proved highly satisfactory:

1. Use an indwelling catheter (Foley bag) with dependent drainage for approximately one week following operation. Use a straight catheter when concerned about pressure (from Foley bag) on operative site.

2. Place the patient in the prone position on a split mattress for 24 to 48 hours, after which the patient may be up and about or lie on either side on a regular mattress.

3. Plenty of fluids and regular diet may be given as desired in order to maintain normal body physiology and improve the patient's healing ability.

4. Oral estrogen may be used to stimulate growth and healing of the vaginal mucosa.

Observance of the precepts here outlined has served us well in the correction of common fistulas of the lower urinary tract in women. Obviously, some modification may be necessary to fit special problems, especially some of the more severe injuries sustained as a result of automobile accidents, or neoplastic invasion of the lower urinary tract. We have not attempted completely to cover lower urinary tract injuries in detail; however, the principles here outlined will be found useful in the management of most such injuries.

While this report deals primarily with our own experience with injuries to the lower urinary tract in women we wish to acknowledge the valuable work

of others whose reports, studies, and suggestions have appeared in the literature from time to time. Our own experience has taught us many things about the repair of fistulas, but the principles here presented are also based on the reported experience of others. To all who have contributed to the study of these problems and thereby aided in their present-day satisfactory management, we too acknowledge our indebtedness.

## FORMULATION OF PRINCIPLES OF TREATMENT IN UTERINE PROLAPSE

LOUIS E. PHANEUF, M.D., Sc.D.,† BOSTON, MASS.

UTERINE prolapse, with its accompanying complications, such as cystocele, rectocele, and enterocele, has existed since women began to bear children. While prolapse may occur occasionally in the nulliparous patient as the result of a congenitally deep cul-de-sac of Douglas, against which intra abdominal pressure is directed, the etiological factor responsible for this disorder, in a large number of patients, is the trauma of labor.

Improved obstetrics has decreased, without doubt, the number of women so afflicted during the last quarter of a century. The almost entire elimination of the high forceps operation from obstetric practice has played an important role in the reduction in the number of these lesions. A small number of parous women, whose tissues are inelastic and involute poorly after parturition, will always form a group wherein this lesion will be prevalent. I have seen it occur in such patients after a perfectly normal delivery, without any visible laceration. A properly performed episiotomy has also contributed to the diminution in a number of these women. Among the writings of Hippocrates, reference is made to the fact that displacements of the uterus were recognized but it was not until the time of Galen, A.D. 130 to 210, that this condition aroused much interest. Galen also gave a good description of prolapsus uteri.

Originally, prolapsus uteri received but little treatment and this is still true in a number of countries. Various supports in the form of folded towels attached to an abdominal binder were employed and are still in use in certain cases, and innumerable forms of pessaries were employed for the same purpose. At the end of the last century the fitting of a pessary was considered an art, and there is no doubt that this method was responsible for bringing some degree of relief to a number of women. With the advent of anesthesia, antisepsis, and asepsis, operative procedures for the problem of prolapse of the rectum and cystocele were considered. According to William Fletcher Shaw,<sup>1</sup> Marshall Hall of London seems to have been the first to suggest narrowing the vagina in the management of uterine prolapse, but it is not recorded that he performed the operation himself. In 1831 Heming operated on the anterior vaginal wall and gave the impetus to numerous other surgeons, who did likewise. Among these are found Marion Sims, Emmet, Aveling, and Gaillard Thomas. The posterior vaginal wall and perineum were repaired by Hegar, Sims, Emmet, Martin, and others. Amputation of the cervix was performed by Huguier, Coupil, Sims, and others. In 1877, Leon LeFort proposed his operation which is a subtotal colpectomy, but which has the serious disad-

†Died Sept. 20, 1953.

vantage of ending sexual intercourse. It is therefore applicable only to women advanced in age, in whom the sexual function can be disregarded, and it still finds a small place in modern gynecological practice.

Anterior colporrhaphy, posterior colporrhaphy, and perineorrhaphy and amputation of the cervix were usually performed singly until 1888 when they were combined by some members of the staff of the Women's Hospital attached to the University of Berlin and by A. Donald of Manchester, working independently. Donald performed his first three operations on April 28, July 18, and Aug. 3, 1888. In the first two he used silver wire as suture material, in the third he used catgut, sterilized in carbolic oil, for the deep tissues and silver wire in the superficial tissues. He had obtained the catgut from Germany where it was used in general surgery. Donald's denudation on the anterior vaginal wall was diamond shaped. This denudation was later modified by W. E. Fothergill by making it triangular in form, with the apex of the triangle below the urinary meatus, and with a wide base near the cervix. By a circular incision around the cervix he combined the amputation of this organ with an anterior colporrhaphy. This produced wide exposure of the bases of the broad ligaments on each side of the cervix, permitting better and stronger apposition of these structures in front of the cervix.

The 1890 edition of Hart and Barbour contains this statement about perineorrhaphy: "These operations help, at least by enabling the patient to wear a ring pessary," and apparently that was the object for which the operation was performed. During the last decade of the nineteenth century, and during the first two decades of the present century, the combined vaginal and abdominal operation in the management of uterine prolapse was popular in many parts of the country, notably in Boston. During the childbearing age it consisted of a dilatation and curettage, tracheolorrhaphy, anterior and posterior colporrhaphy and perineorrhaphy for the vaginal part, while abdominally the uterosacral ligaments were shortened and a round ligament suspension of the uterus was performed. After the menopause, an amputation of the cervix was resorted to instead of a trachelorrhaphy and an abdominal fixation of the uterus replaced the suspension. In cases of prolapsus uteri, in which future pregnancy was eliminated, ventrofixation of the uterus was a common procedure at the end of the nineteenth century. The method of implantation of the uterus in the abdominal wall became prominent at this time. The Harris procedure, with repair of the pelvic floor, was frequently employed at that time. In the Harris method the rectus fascia is sutured to the anterior surface of the uterus. In the Kocher operation the uterus is brought through all layers of abdominal wall except the skin. The different layers of the wall are sutured to the uterus and the skin is closed over it. The Murphy method consisted of suturing the uterus into the lower part of the abdominal wall. The lateral structures are clamped, divided, and ligated, to free the corpus uteri which is bisected, and the uterine mucosa is excised. After the excision of the mucosa the two halves of the uterine corpus are turned out and fastened securely to the upper surface of the rectus aponeurosis by firm sutures and the operation is completed by closing the skin.



Another method of treating uterine prolapse at that time consisted of performing a supravaginal hysterectomy with fixation of the lateral pedicles to the cervix, or by fixing the cervix to the abdominal wall. After a total hysterectomy the lateral pedicles of the vagina or the vagina itself were sutured to the abdominal wall. These methods of fixation of the uterus or its incorporation in the abdominal wall are very seldom resorted to at the present time.

On Jan. 28, 1898, Thomas J. Watkins<sup>2</sup> performed his first so-called interposition operation. This was intended for the patient, after the menopause, who had a large cystocele and prolapse of the uterus in the first and second degrees. It was not intended for third-degree prolapse of an atrophic uterus, nor was it recommended in the presence of uterine or concomitant pathology. This procedure, to which the name of "transposition operation" was applied by its originator in 1921, enjoyed great popularity during the first three decades of the present century. It has been replaced largely by the Manchester operation or vaginal hysterectomy with plastic repair. It is still a very useful operation in well-selected cases.

According to Ricci,<sup>3</sup> the first vaginal hysterectomy for a prolapse was performed by Samuel Choppin of New Orleans on Jan. 12, 1861, and the second vaginal hysterectomy for prolapse by A. Patterson, who reported on it in the *Glasgow Medical Journal* in 1876. While J. Riddle Goffe proposed vaginal hysterectomy and vaginal plastics for prolapse and cystocele and gave the operation to the profession before C. H. Mayo, it was the latter who popularized the method and made it an accepted procedure in the management of this condition. In 1914, C. H. Mayo read an article on uterine prolapse and cystocele before a meeting of the Southern Surgical Association in Asheville, North Carolina. He proposed the performance of vaginal hysterectomy with complete approximation of the broad ligaments in the median line. Vaginal hysterectomy with lateral fixation of the broad-ligament pedicles has replaced the Goffe and Mayo types of operations in several clinics at this time.

In the performance of operations for prolapsus uteri and cystocele there are two schools of thought. There are those who believe that the uterus should be conserved whenever possible since, if recurrence should be the result, it would be attended to with greater success when the uterus is present than when the opposite obtains; then there are those, who seem to be increasing in number, who prefer to remove the uterus when operating for this condition. The main complications which develop after vaginal hysterectomy are a hernia of the cul-de-sac of Douglas, otherwise known as an enterocele, and, in some cases, inversion of the vagina.

Table I, published in the *Journal international de chirurgie*,<sup>4</sup> shows the various methods that I have employed in operating on my 1,066 cases of prolapse up to Aug. 1, 1952.

### Summary

In summary, in my own practice the management of prolapse and cystocele is largely the following: In the younger women still in the childbearing age,

TABLE I. OPERATIONS IN UTERINE PROLAPSE, 1,066 CASES

TYPE OF OPERATION	NO. OF CASES
Vaginal plastic repair and suspension of uterus	137
Interposition operation	256
Vaginal hysterectomy and vaginal plastics	251
Vaginal hysterectomy (clamp method)	41
Fundic vaginal hysterectomy, with or without amputation of the cervix, and interposition of remaining uterus	21
High vaginal fixation of uterus	66
Manchester (Fothergill operation)	130
Subtotal colectomy (LeFort operation)	33
Total colectomy	10
Operation for posterior vaginal enterocele	86
Anterior and posterior colporrhaphy and perineorrhaphy	3
Amputation of cervix, anterior and posterior colporrhaphy and perineorrhaphy	3
High amputation of cervix for infravaginal hypertrophy	3
Interposition of prolapsed cervical stump following supracervical hysterectomy	1
Vaginal trachelectomy for prolapse of cervical stump following supracervical hysterectomy	17
Vaginal plastics, supracervical hysterectomy, and fixation of pedicles to cervix	2
Abdominal fixation of uterus for vaginal prolapse	1
Amputation of cervix and uterine suspension	2
Abdominal panhysterectomy and fixation of pedicles to vaginal cuff	2
Suspension of the uterus	1
Total	1,066

dilatation and curettage, trachelorrhaphy, anterior and posterior colporrhaphy, perineorrhaphy, shortening of the uterosacral ligaments, and round-ligament suspension of the uterus. In those patients who are postmenopausal, the Manchester operation when the uterus can be saved, the interposition operation in an occasional suitable case, and vaginal hysterectomy with lateral fixation of the pedicles, together with vaginal plastics. The operation of colpocleisis, partial or total, is reserved for those who have inversion of the vagina.

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## FINAL THOUGHTS ON THE MANCHESTER OPERATION OF COLPORRHAPHY FOR GENITAL PROLAPSE

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ALTHOUGH retired from practice for some years, and never again expecting to write on a clinical subject, I cannot resist the subtle flattery of being asked to contribute to this *Festschrift* in honor of my old friend George W. Kosmak, who has done so much, through his long editorship of the AMERICAN JOURNAL, for world, as well as for American, obstetrics and gynecology.

It is now twenty-one years since he honored me by publishing in this JOURNAL a paper in which I described the plastic operation for prolapsus uteri which for so long had been performed in Manchester, and which I suggested in that paper should be designated the "Manchester operation" rather than by the name of any one operator. My reason for suggesting this change of name was the confusion over it, even in Manchester itself. As the operation has been much improved by succeeding Manchester operators, and it was too late to attempt to attach to it the name of the inventor, Donald, I suggested this geographical title, the name of the city in which it has been performed almost exclusively for the treatment of this common condition since 1888.

In that year Archibald Donald was appointed to the Honorary Staff of St. Mary's Hospital, Manchester, and, as so many obstacles had to be overcome before he was able to undertake abdominal surgery as fully as he desired, he turned his attention to the cure of this ancient disabling condition in women, prolapsus uteri, a condition of special frequency and severity in this city where there was such a high percentage of female labor.

Before that time, many attempts had been made to cure or alleviate the condition by operative means, anterior colporrhaphy, posterior colporrhaphy, and perineorrhaphy, amputation of the cervix, and even vaginal hysterectomy. Some of these were successful, at least in alleviating in part the distressing condition, but none could show a high percentage of cures. Donald decided to combine these methods, amputation of the cervix with anterior and posterior colporrhaphy, and very soon laid emphasis upon the suturing of the deep tissues as the most important step in the operation. At first he had to use silver wire, but, after his first three cases, all successful, he was able to obtain a supply of catgut sterilized in carbolic oil from Germany which from that date he used to the exclusion of all other suture material, though for many years he experimented with various methods of preparation until he obtained one which could be relied upon to sterilize the gut and to leave it strong and pliable.

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About the same time Oldhausen and Schröder in Germany, quite independently, were experimenting with the same combination of operations, but this fell into disuse, and does not seem to have been adopted by other German operators. Not so with Donald's operation. When I became his House Surgeon in 1904, not only was the combined operation the only treatment for this condition used by Donald and his juniors, but, what was more remarkable, the only treatment employed by his seniors. So universal was the operation in St. Mary's Hospital, and so good were the results, that it was somewhat of a shock, when I left there five years later, to find that it was not universal in other centers, and in fact that many had not heard of it. Donald unfortunately did little writing, which he scorned as a form of self-advertisement, and therefore hoped to propagate his gospel by demonstrating the operation to the numerous gynecologists who came to watch him.

In 1906, through the amalgamation of the Southern Hospital with St. Mary's Hospital, Fothergill came onto the combined staff, and for the first time saw the operation. He was an able man, with a sound scientific training and great facility for writing. He was much impressed by the operation and bent his mind to the study of the underlying principles, publishing in 1907 a paper on the supports of the pelvic viscera. From this he progressed to altering the lines of the incision of the anterior colporrhaphy and to making them continuous with that for the amputation of the cervix, which allowed of better access to the deep pelvic tissues, with greater certainty of suturing them, and eliminated the bridge of tissue left between the cervix and anterior colporrhaphy by Donald's incision. In this way, Manchester gynecologists began to speak of Fothergill's modification of Donald's operation, and soon, for brevity, of Fothergill's operation, with the result that the name of the original operator was displaced by that of one who had merely modified the operation and written extensively about it. Successors have made modifications; in fact, few carry out the operation exactly like their colleagues, some finding it easier to expose the important tissues and to insert the vital sutures in one way, others with some slight modification, but so long as anterior and posterior colporrhaphy are combined with amputation of the cervix, and the deep pelvic tissues are sutured in front of and behind the cervix, it is the operation performed in Manchester, and it seemed reasonable to use this generic nomenclature.

The operation was fully described and illustrated in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, Vol. 26, November, 1933, and I do not propose to take up space in this short article with a repetition, as the general principles have not altered since that date. Rather, I wish to concentrate upon some aspects about which there has been controversy.

I understand that since 1933 this operation has been on trial in many centers in the United States, and this is confirmed by the articles and references which have appeared in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, which give the impression that it is used in many hospitals, but only for a certain type of genital prolapse, as this condition seems to be divided into watertight compartments according to age or degree, and one specific operation used for each class.



### Vaginal Hysterectomy

To me this is inexplicable, especially as the majority of critics state that they do not use the Manchester operation in elderly women. Why, I cannot understand, as I found that old women, as a class, gave the highest percentage of cures. No, for some reason I cannot understand, in the United States and in some centers in my own country, it is the fashion now to combine the colporrhaphy with vaginal hysterectomy and to consider the latter an important factor in the cure.

Every now and again my old friend Novak takes me to task for my statement that vaginal hysterectomy has no part in the cure of prolapsus uteri. I am still completely unrepentant, and repeat it. Vaginal hysterectomy is very easily performed in combination with colporrhaphy, and when I desired to remove the uterus, as well as to cure genital prolapse, I frequently did so, but I always emphasised the fact that I was combining two separate operations and that the vaginal hysterectomy had no part in the cure of the prolapse. Some operators claim that with hysterectomy there is better exposure of the deep pelvic tissues, and therefore greater ease in suturing them to close the gap in the pelvic floor. This simply means that the hysterectomy makes it easier for them to carry out the essential steps of the operation. Personally, I never found any real difficulty in exposing and suturing the essential tissues, and in elderly women, when the tissues have atrophied, I found it more satisfactory to retain the uterine tissue, using it, as Donald used to say, like a cork in a bottle.

To those who advocate vaginal hysterectomy as part of the cure of genital prolapse, I would ask: Have they ever relied upon vaginal hysterectomy alone?

The amalgamation of the two hospitals in Manchester in 1906, which brought Fothergill into contact with Donald, also brought the senior surgeon of the Southern Hospital onto the combined staff. He was beyond the age when the reception of new ideas is easy, and, moreover, anything connected with St. Mary's Hospital was anathema to him, so he continued to treat the severe cases of genital prolapse by vaginal hysterectomy. A few years later I succeeded him on the staff, and spent much of my time trying to cure the cases of genital prolapse in women whose uteri had already been removed by vaginal hysterectomy, a much more difficult task than in women whose uteri are still present.

No, I am still unrepentant. Vaginal hysterectomy can easily be performed along with colporrhaphy, and to some operators it may seem to give easier access to the deep tissues, but I still maintain that it has no part in the cure of genital prolapse.

### Amputation of the Cervix

In recent years there has been criticism of amputation of the cervix, especially in young women who may expect to have further labors, as dystocia may follow. I can only say that in the forty and more years in which I was attached to St. Mary's Hospital, when all the staff were treating prolapse by this combined Manchester operation, I never met with a single case of dystocia. This is not to deny that other operators may have met with an occasional one. In

these, I wonder how the cervix was sutured. I believe that the vaginal skin should be sutured carefully to the edge of the cervical canal, so as to leave as neat a wound as possible with less risk of forming extensive scar tissue. Whether this is the real answer I cannot say, as I have not met with dystocia, and I am doubtful whether it does occur with any frequency, as all the cases of which I have read are published as rarities.

The opposite extreme, abortion or premature labor, unfortunately may follow, and is more frequent the higher the amputation. I feel, therefore, that in young women as small a piece of cervix should be removed as will allow of repair to the cervix, and even no amputation when the cervix seems to be undamaged, though I was rarely quite satisfied with the results in these cases, the nonamputated cervix seeming to protrude too far into the vagina, and it might be better, as Hunter has since suggested, to remove a cuff of vaginal wall from around the cervix and so elevate the external os.

### Stress Incontinence

In the last few years much attention has been given to this condition and for a time various sling operations were fashionable. In the majority of cases with this distressing condition, a colporrhaphy, with special care to suture the deep pelvic tissues in the region of the neck of the bladder and along the length of the urethra, effects a cure. There are, however, a few cases of failure, which may be cured by a sling operation, but the number of sling operations performed during the years of its fashion were out of all proportion to the number of failures after colporrhaphy. If the latter operation had been performed with special attention to the deep sutures, I believe there would have been few failures, and fewer recurrences than apparently occur after sling operations.

In the series of colporrhaphies whose after-histories I published, I found that the majority of patients with stress incontinence after the operation stated that they had suffered from it before the operation, but as the disability was so much less than from the prolapsus uteri, they had not mentioned it. In these cases no special care had been taken to suture the deep structures behind the base of the bladder and along the urethra, as I always did when the patient complained of stress incontinence, and doing this as a second operation cured the majority of these.

Jeffcoate and Roberts have pointed out that stress incontinence is due to the obliteration of the angle between the insertion of the urethra and the bladder wall, and their suggestion is supported by x-ray photographs.

Following along this line, Bailey of Manchester has evolved an addition to the usual Manchester operation whereby the vaginal walls are sutured to the pubovaginalis muscle, thereby increasing the urethrovesical angle, the only drawback to the operation being the necessity of making a suprapubic incision to expose the urethra and muscle. I am purposely not giving any description of this, as his article will be published early this year in the *Journal of Obstetrics and Gynaecology of the British Empire*.

The symptom "stress incontinence" has a somewhat elastic interpretation, and an enthusiastic house officer will elicit it from most parous patients. This probably accounts for the very large number of sling operations performed in recent years, numbers out of all proportion to the percentage who complained of this condition when I was in active practice. This is not to say that I, and my contemporaries, may not have underestimated it by overlooking a number of cases where the symptoms were slight and therefore not complained about by the patient, or sought for by the investigator.

If elimination of the angle between the bladder and insertion of the urethra is accepted as proof of stress incontinence, this can in itself be proved by x-ray examination. I have examined a considerable number of x-ray photographs which do confirm this suggestion, and I think it may be used to differentiate the real cases of stress incontinence from the fictitious ones. Acting on this assumption, Bailey performs his combined operation only upon those with obliteration of this angle. In those whose postoperative results I have been privileged to investigate, the angle has been restored by the operation and the patients have been cured. It is possible that careful deep suturing of the pelvic floor exposed by the anterior colporrhaphy may restore the angle in many cases, but where the angle is definitely lost, there is a very strong argument for this addition to the operation.

### Enterocoele

Each time I reviewed a long series of patients upon whom I had performed this Manchester operation, there were few who complained that they were not cured, or that the condition had recurred, and, of this small number, almost invariably the trouble was due to an enterocoele; practically never did the cervix and pelvic floor descend. From the patient's point of view it makes little difference whether the "something coming down" complained of is the cervix or a piece of vaginal skin, but scientifically it is satisfactory to know that the pelvic floor itself can be so effectively sutured without removal of the uterus that laxity of these tissues practically never recurs.

An enterocoele is easily cured by a second operation, but it is a second operation to the patient, and equally dreaded, whatever its extent. In latter years my chief endeavor was to prevent it by carrying the incision of the posterior colporrhaphy as high as possible, practically to the cervix, and then separating the rectum and peritoneum completely from the vaginal wall before closing the gap in the musculature. Great care in suturing these muscles up to the level of the cervix should prevent this, but a little carelessness is liable to be punished by an enterocoele. Read and others suggest ligating and excising the peritoneal sac and I would do this if I were still operating, before suturing the deep muscles.

I wish I could persuade my American friends to cease to divide genital prolapse into water-tight compartments according to age, parity, etc. Essentially the condition is the same and is produced in the same way whatever the age of the patient or the degree of the prolapse, and the only difference between parity and nulliparity is that in one the weakness of the tissues is due to damage, while

in the other the cause is developmental weakness combined with increased intra-abdominal pressure, usually from physical hard work.

In my experience, a higher proportion of postmenopausal women were cured than those of an earlier age, and in neither was the sacrifice of the uterus necessary unless there was a pathological condition which called for its removal. Even then the cure was not, in my opinion, due to the hysterectomy, and would have been equally good if the uterus had been retained.

Looking back over a professional life of over half a century, no operation has rewarded me so well and so consistently as has the Manchester operation for genital prolapse, and I think my Manchester colleagues, seniors, contemporaries, and juniors, will agree with me. For more than seventy-five years this disablement, at all ages, of all degrees, and in all social conditions, has been treated with this operation with invariably good results.

No conservative operation for any condition can give a hundred per cent of cures, but, in my experience, this operation comes as near perfection as any treatment for any condition to which human flesh is heir.

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## MAJOR GYNECOLOGICAL SURGERY IN THE AGED PATIENT

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MAJOR surgical procedures in the aged patient are a matter of increasing importance to the gynecologist. This is partially due to the growing numbers of persons reaching the older age groups. People over 65 years of age made up less than 3 per cent of the population in 1850, and in 1930 amounted to 5 per cent of the census. In 1950 this proportion rose to 8 per cent, and by 1980 it is estimated that this age group will constitute more than 10 per cent of the population. The principal factor in this shift, reduction of infant mortality, is approaching an irreducible minimum, but the over-all lowering of mortality in all age groups may be expected to continue this trend for some time to come. The gynecological problems of the elderly patient, therefore, will be encountered with mounting frequency in future years.

There has also been a growing acceptance of the aged patient as a candidate for major surgery. With the advent of antibiotics, the ready availability of blood, and the careful evaluation of anesthetic techniques, major operations of considerable extent can be carried out with relative safety in elderly patients. Numerous studies in the literature show that this has been recognized for some time by general surgeons, who have made pleas for earlier operation where surgery can offer cure or substantial palliation in this age group.<sup>1</sup> It should be pointed out that the reported higher mortality rates are in large part due to the increased incidence of malignant disease in patients of advanced years. The hazards of emergency surgery at this time of life are also greater than in young individuals.<sup>2</sup>

Major gynecological surgery in the aged patient may be considered in two broad categories. Abdominal surgery is usually performed for proved or suspected malignancy. Here the indications for operation transcend minor considerations of surgical risk. Extensive procedures may be attempted in the hope of a cure or substantial palliation, where there is no effective alternative treatment, with an expected increase in mortality and complications. Vaginal surgery is usually carried out for the relief of distressing symptoms. These procedures are seldom lifesaving, and their value to the patient in terms of relief and rehabilitation should be considered carefully along with the prospective hazards of operation. That this type of surgery may be carried out safely in elderly patients has been shown by Phaneuf,<sup>3</sup> and more recently by Payne.<sup>4</sup> The wide diversity of vaginal operations which can be adapted to fit the individual case makes this an important means of treatment in the elderly patient.

The age of 65 is generally employed as the lower limit in discussion of aged patients, since most persons show evidence of physiological aging by this time of life. It has been noted by some authors that roughly half of their patients fall between the ages of 65 and 69; suggestions have been made to consider only patients of 70 years or over in order to demonstrate more clearly the problems of surgery in the later years.<sup>1</sup> In the male, this limit has been raised to 80 in a study of transurethral resection in the aged.<sup>5</sup> Other writers have been content to use the age of 60 as a border line, with an expected decrease in mortality and complications.

This report deals with 139 major gynecological operations performed on 131 patients over the age of 65 on the gynecological service of Bellevue Hospital from June, 1941, through December, 1953. There were nine deaths, an operative mortality of 6.5 per cent. The incidence of these procedures among major operations on the entire service is shown by years in Table I. The average is 3.1 per cent, with little variation during the last decade.

TABLE I. INCIDENCE OF MAJOR GYNECOLOGICAL SURGERY IN AGED PATIENTS

YEAR*	TOTAL MAJOR OPERATIONS	MAJOR OPERATIONS IN AGED PATIENTS	PERCENTAGE
1941	469	1	0.4
1942	360	6	1.7
1943	292	5	1.7
1944	303	10	3.3
1945	309	13	4.2
1946	335	9	2.7
1947	333	10	3.0
1948	377	13	3.4
1949	376	24	6.4
1950	380	14	3.7
1951	368	14	3.8
1952	370	14	3.8
1953	178	6	3.3
Total	4,450	139	3.1

\*Annual figures for a year beginning June 1. Figures for 1953 are for six months only.

*Age, Race, and Parity.*—Sixty-six, or roughly 50 per cent of these patients, were less than 70 years old. Ten patients were over 80, and in this group there were four operative deaths, two of which were related to malignant disease. The operative mortality for patients less than 70 years old (65 to 69) was 2.7 per cent. The oldest patient, aged 95, tolerated vaginal hysterectomy without difficulty. There were 21 nulliparas, and one of these complained of symptoms ref-

TABLE II. AGE, RACE, AND PARITY

AGE GROUP (YEARS)	NO. OF PATIENTS
65-69	66
70-74	35
75-79	20
80-89	9
90 and over	1
Total	131
White	114
Negro	17
Nulliparas	21
Multiparas	110



erable to prolapse of the uterus. One hundred fourteen patients were white, and 17 Negro (Table II).

*Complaints.*—The majority of complaints were associated with prolapse of the uterus, ranging in duration from three weeks to more than fifty years. Postmenopausal bleeding, a relatively common complaint, was associated with uterine malignancy in only 9 of 26 cases. Stress incontinence was a presenting complaint in 19 instances, but was probably far more frequent as a minor complaint than this would indicate. Stress incontinence of a minor degree was present in many patients who did not complain of it at all. Pruritus of the vulva was the complaint in 7 of the 8 cases of leukoplakia of the vulva, and in two instances of vulvar carcinoma. In two patients routine physical examination led to the discovery of abdominal masses requiring laparotomy (Table III).

TABLE III. CHIEF COMPLAINTS

Prolapse of uterus	60
Vaginal bleeding	26
Abdominal pain	21
Stress incontinence	19
Abdominal mass and swelling	12
Pruritus of vulva	8
Weakness	3
Nausea and vomiting	2
Back pain	2
Sensation of weight in pelvis	5
Vulvar mass	2
Weight loss	2
Anorexia	1
No complaint	2

*Medical Status.*—The general physical condition of these patients was of particular interest since in patients not suspected of having malignant disease this is one of the determining factors in a decision to perform major surgery. The medical status of each patient was evaluated by physical examination and by routine blood and urine studies on admission. In addition, the opinion of a medical consultant was obtained in 80 cases, while no consultation was requested in 51 cases. Most of these consultations were requested for the evaluation of hypertension or cardiovascular disease, or both, and led to x-ray and electrocardiographic studies. The opinion of the consultant was phrased in terms of risk of the prospective procedure to the patient, with suggestions as to care during and after operation, and occasionally recommendations regarding anesthesia. In each case, however, the decision to perform major surgery was in the hands of the gynecologist.

Table IV shows the diagnoses in these patients, aside from the gynecological condition. Hypertension or some form of cardiovascular disease was the most common medical diagnosis, and was the most frequent reason for consultation. Although no arbitrary rule was followed, hypertension of mild or moderate degree was not regarded as a large hazard to surgery, and caution against a sudden drop in blood pressure was usually the only recommendation made. Obesity was a prominent finding in 28 cases, though the charts of

TABLE IV. MEDICAL STATUS

Medical consultation prior to operation	80
No medical consultation	51
<i>Medical Diagnosis.—</i>	
Essential hypertension	43
Hypertensive cardiovascular disease	36
Obesity	28
Arteriosclerotic cardiovascular disease	22
Generalized arteriosclerosis	10
Diabetes mellitus	9
Arthritis	5
Pulmonary fibrosis and emphysema	4
Bronchopneumonia	4
Asthma	3
Thyroid adenoma	2
Bronchitis	2
Cachexia	2
Senile psychosis	2
Epilepsy	2
Rheumatic heart disease	2
Sarcoma of arm	1
Hepatomegaly	1
Duodenal ulcer	1
Hydronephrosis	1
Hypothyroidism	1
Severe anemia	1
Aneurysm of carotid artery	1
Digitalized preoperatively as a prophylactic measure	9

these patients indicate that many more were overweight. There were 9 cases of diabetes, but difficulty in control was encountered only once. Nine patients were digitalized as a prophylactic measure before operation.

*Operation.*—Forty-seven abdominal procedures were carried out. These included 20 hysterectomies, 12 total and 8 of the supracervical type. Among the latter the cervix was left in usually to shorten an otherwise lengthy or difficult operation. Five radical operations were done, including one pelvic extenteration, one partial colectomy and pelvic lymph node dissection, and three groin dissections of the Basset type. In two patients in this group abdominal operation was carried out for the relief of stress incontinence, while in the remainder the indication was suspected or proved malignancy. There were five deaths, an operative mortality of 10.6 per cent. Four of these occurred in cases of malignant disease, and the fifth following emergency laparotomy for an enormous ovarian cyst.

There were 92 vaginal operations, including 10 vulvectomies. A wide diversity of procedures was employed, as shown in Table V. This varies considerably from the choice of procedures reported by other authors,<sup>4</sup> and in addition there has been variation in policy on this service. During the first seven years of the period covered by this report, the LeFort operation was performed 13 times for uterine prolapse, and during the same period of time there were 6 vaginal hysterectomies. The last LeFort operation was done in May, 1948, and since that time 33 vaginal hysterectomies have been done. The Watkins interposition operation was employed only once, and the Manchester (Fothergill) procedure 7 times. Vaginal hysterectomy was carried

out twice for uterine malignancy, in patients with marked obesity, in whom varying degrees of prolapse made the vaginal approach by far the safest.

There were four deaths following vaginal or vulvar operations, a mortality of 4.3 per cent. Three of these followed vaginal hysterectomy or colpoceleisis for benign indications, and will be discussed later. The fourth followed vulvectomy in a diabetic patient with carcinoma of the vulva.

**Operating Time.**—In most discussions of the principles and technique of major surgery in the aged, one finds the recommendation that prolonged operations be avoided. This has also been advanced as a reason for preference of one type of vaginal procedure over another. As shown in Table VI, three-fourths of the operations in this report were accomplished in 1½ hours or less. Most of them were carried out by the resident staff, with the assistance of an attending gynecologist. A study of the longer procedures reveals no apparent relation to postoperative complications or mortality.

TABLE V. TYPE OF OPERATION

<i>I. Abdominal Procedures.</i> —	
Total hysterectomy, with or without removal of adnexa	12
Supracervical hysterectomy, bilateral salpingo-oophorectomy	8
Salpingo-oophorectomy and oophorectomy	16
Secondary closure of abdominal wound	2
Basset dissection of inguinal and femoral nodes	3
Fascial sling operation for stress incontinence	1
Vesicourethral suspension	1
Partial colpectomy and pelvic node dissection	1
Exploratory laparotomy, removal of omental tissue	2
Pelvic exenteration	1
Total	47
<i>II. Vaginal and Vulvar Procedures.</i> —	
Vaginal hysterectomy	1
Vaginal hysterectomy, salpingo-oophorectomy	3
Vaginal hysterectomy, anterior and posterior wall repair	32
Vaginal hysterectomy, repair of enterocele	2
Vaginal hysterectomy, simple vulvectomy	1
Manchester (Fothergill) operation and repair	7
Anterior and posterior colporrhaphy, perineorrhaphy	16
Anterior and posterior colporrhaphy, vulvectomy	1
Anterior and posterior colporrhaphy, repair of enterocele	3
Watkins interposition operation	1
LeFort operation	13
Excision of vaginal tumor	2
Vulvectomy	7
Partial vulvectomy	3
Total	92
<i>Operative Accidents.</i> —	
Severed ureter	2
Laceration of bowel	1

**Anesthesia.**—Knight has summarized the principles of geriatric anesthesia, with the conclusion that any proved anesthetic agent or technique is suitable for aged persons, if given with proper precautions and requisite skill. Payne<sup>4</sup> preferred spinal anesthesia for vaginal surgery. In this series more than half of the patients were anesthetized with cyclopropane, with ether the next most common agent. Local or regional anesthesia was employed seldom, usually in

cases of high risk (Table VII). Serious anesthetic difficulty was encountered twice, in both instances with spinal anesthesia. In one case a 67-year-old woman tolerated caudal anesthesia well for an anterior colporrhaphy. She continued to suffer from stress incontinence, and was readmitted for a fascial sling operation. On this occasion she went into shock following spinal anesthesia, and was revived and returned to the ward without operation. In a second case spinal anesthesia was given for secondary closure of a wound dehiscence on the seventh postoperative day. Anesthesia was inadequate, and, despite a recent meal, cyclopropane anesthesia was begun. The patient vomited, aspirated, required bronchoscopy, and was finally returned to the ward in fair condition. This patient, aged 71, recovered after a stormy course.

TABLE VI. OPERATING TIME

One hour or less	36
1-1½ hours	64
Total 100 (72%)	
1½-2 hours	28
2-2½ hours	7
Over 2½ hours	4
<i>Operations Requiring More Than 1½ Hours.—</i>	
Vaginal	25
Abdominal	11
Vulvar	3
Average operating time for vaginal hysterectomy (with or without colporrhaphy)	105 minutes
Average operating time for LeFort operation (with or without perineal repair)	68 minutes

TABLE VII. ANESTHESIA

Cyclopropane	91
Nitrous oxide, oxygen, ether	24
Spinal	7
Local	4
Continuous caudal	3
Surital and nitrous oxide	2
Cyclopropane and Surital	2
Pentothal	2
Morphine and scopolamine	2
Caudal and nitrous oxide, oxygen, ether	1
Spinal and cyclopropane	1
Total	139

*Postoperative Complications.*—There were surprisingly few complications, in view of the serious condition of some of these patients, and the gravity of the procedures carried out. Table VIII lists the major postoperative complications which required definitive treatment or prolonged the hospital stay. Urinary tract infections were generally controlled or avoided by the use of sulfonamides in all patients with indwelling catheters. Three-fourths of these patients received antibiotics during the postoperative course. All but one of the wound infections occurred in patients subjected to radical vulvectomy and groin dissection for vulvar carcinoma. Two rectovaginal fistulas following



posterior colporrhaphy occurred, and in both cases spontaneous closure was noted within 4 months. There were two wound dehiscences, requiring secondary closure. Hospital stay was prolonged beyond two weeks in 63, or slightly less than half the cases, but it should be noted that these included cases of malignant disease receiving x-ray therapy, vulvectomies, and a number of cases in which social or economic factors made a prolonged stay desirable.

TABLE VIII. POSTOPERATIVE COMPLICATIONS

Cystitis and pyelitis	7
Bronchopneumonia	4
Wound infection	4
Senile psychosis	4
Oliguria and anuria	2
Rectovaginal fistula	2
Coronary thrombosis	2
Wound dehiscence	2
Small bowel volvulus	1
Atonic bladder	1
Uremia	2
Diabetic acidosis	1
Cardiac failure	1
Paralytic ileus	1
Residual urine of more than 100 c.c. ten days following vaginal surgery	6
Persistent stress incontinence	3

TABLE IX. MAJOR PATHOLOGICAL FINDINGS

Atrophic uterus	34
Fibromyoma of the uterus	14
Adenomyosis interna	9
Sarcoma of the uterus	1
Sarcomatous degeneration of fibroid	1
Carcinoma of the cervix	1
Leukoplakia of the cervix, with carcinomatous change	1
Carcinoma of the ovary	6
Pseudomucinous cystadenoma	4
Pseudomucinous cystadenocarcinoma	2
Papillary serous cystadenoma	2
Papillary serous cystadenocarcinoma	2
Serous cystadenoma with torsion	1
Dermoid cyst with theca-cell tumor	1
Dermoid cyst with squamous carcinoma	1
Parovarian cyst	2
Fibromyoma of ovary	1
Theca-cell tumor of ovary	1
Tuberculosis of ovary	1
Fibroma of ovary	1
Leukoplakia of vulva	6
Leukoplakia of vulva with carcinomatous change	2
Squamous-cell carcinoma of vulva	4
Squamous-cell carcinoma of vagina	2

In general, no unusual postoperative care was given, and the usual postoperative regimen of the ward was adhered to. The majority of patients were ambulated within a few days of operation. It is believed that the relatively smooth postoperative course in most of these cases is evidence of the tolerance and resilience of the patients themselves, rather than of any extensive preoperative preparation or special postoperative care.

*Pathological Findings.*—The pathology encountered in this advanced age group is interesting because of the high incidence of neoplastic disease. The conditions are listed in Table IX. There were 11 malignant ovarian tumors, the majority of which were of an undifferentiated variety. Among the benign

TABLE X. POSTOPERATIVE DEATHS

CASE	AGE	OPERATION	COURSE	FINAL CLINICAL AND PATHOLOGICAL DIAGNOSIS
1. D. M.	76	Supracervical hysterectomy, bilateral salpingo-oophorectomy	Wound dehiscence Paralytic ileus Septic course Progressive oliguria Shock Died on eighth postoperative day	Carcinoma of the ovary with peritoneal spread
2. H. P.	86	Exploratory laparotomy	Shock, died 16 hours after operation	Carcinoma of the stomach with widespread metastases
3. M. C.	73	Emergency laparotomy Left salpingo-oophorectomy	Cardiac failure Anuria Uremia Wound infection Died on eighth postoperative day	Cardiac failure and uremia 53 pound tumor of ovary Pseudomucinous cystadenoma with hemorrhage, necrosis, and infection
4. C. B.	68	Total abdominal hysterectomy Bilateral salpingo-oophorectomy	Intestinal obstruction Shock Died on eighth postoperative day	Small bowel volvulus Sarcomatous degeneration of fibromyoma Theca-cell tumor
5. F. L.	67	LeFort operation	Uneventful immediate recovery Died suddenly on sixth postoperative day	Coronary thrombosis (clinical impression)
6. S. E.	82	Vaginal hysterectomy Anterior and posterior colporrhaphy Perineorrhaphy Repair of enterocele	Immediate postoperative course smooth Died suddenly on ninth postoperative day	Autopsy revealed coronary thrombosis
7. H. S.	85	Vulvectomy	Poorly controlled diabetes, slough of vulvar wound Died suddenly on thirty-fourth postoperative day	Carcinoma of the vulva Coronary thrombosis (clinical impression)
8. S. N.	87	Vaginal hysterectomy Anterior and posterior colporrhaphy Perineorrhaphy	Senile psychosis Died on forty-ninth postoperative day after condition slowly deteriorated	Malnutrition Cachexia Senile psychosis
9. L. R.	70	Pelvic exenteration	Recovered from immediate effects of surgery Wet colostomy functioned but patient adjusted poorly to loss of sphincters and became nursing problem Died on sixty-ninth postoperative day	Autopsy revealed carcinoma of the cervix, recurrent, with widespread metastases

ovarian tumors were two large pseudomucinous cystadenomas, which weighed 53 and 42 pounds. The cervix of the oldest patient, aged 95, showed a bizarre lesion. This patient's menopause occurred before the turn of the century, and she stated that she had had symptoms of prolapse for fifty years. The cervix had a pearly white appearance with deep cracks and fissures, and sections showed a marked degree of keratinization with carcinomatous change and invasion of underlying stroma.

*Postoperative Deaths.*—Table X shows, in tabular form, the details of the 9 patients who died following operation. While these have all been included in calculation of mortality already referred to, it seems logical to divide them into categories according to the relation between operation and subsequent death. Cases 1 to 4 may properly be classed as operative deaths, for the patient never recovered physiologically and her condition deteriorated progressively, with death in 1 to 8 days. Three of these patients suffered from malignancy, and the fourth had a large infected ovarian tumor which was histologically benign. Cases 5 and 6 died on the sixth and ninth days, respectively; both had appeared to be doing well in the immediate postoperative period. The terminal episode was sudden, and seemed typical clinically of coronary thrombosis. Autopsy was done in one of these cases. This is a risk which is assumed in every operation at this time of life, but in neither of these cases could death be related directly to operation. In Cases 7, 8, and 9 death occurred more than one month after operation. One patient, 85, died 34 days after vulvectomy for carcinoma. She had diabetes, poorly controlled, and died suddenly. Another patient, 87, became psychotic after a vaginal hysterectomy, and died seven weeks later; she was fed intravenously during most of this period. The last patient had a recurrent carcinoma of the cervix following radiation, with involvement of bladder and rectum. Pelvic exenteration was carried out with the intent of producing cure rather than palliation. This patient recovered from the immediate effects of operation, but died two months later with generalized metastases. In summary, five of these patients had malignant disease, and in four this was widespread.

### Comment

These results indicate that major gynecological surgery can be carried out with relative safety in the aged patient, provided physical and mental status is investigated with care preoperatively, and with due regard for operative and anesthetic technique. The postoperative course is usually remarkably smooth. There is no question of the need for laparotomy in cases of suspected malignancy. Vaginal surgery can be offered to elderly patients as a safe means of relief from distressing symptoms, provided their general condition is good.

Follow-ups were available on less than half of the patients in this series, but in those who returned results were generally excellent. Similar results are reported by Payne.

Conservatism with regard to vaginal surgery, based on age alone, should be exercised in cases of extremely advanced age. In patients who have reached the ninth decade, hazards of operation are greater, life expectancy is shorter, and the possibilities of rehabilitation and return of activity limited. In patients with marked senility, at any age, there is little to be gained from vaginal surgery.

Radical surgery may be attempted in the aged when their physical condition is good, and when the prospects of cure seem to warrant such a procedure. This is especially true when there is no alternative treatment. In doing this it should be remembered that one is producing the ultimate in surgical stress in a patient who is not equipped to tolerate extremes. Aside from the fact that the place of such surgery is still unsettled, it appears logical to restrict these operations in the aged to persons in excellent physical condition in whom the chance of cure is great.

### Conclusions

1. Results of 139 major gynecological surgical procedures in 131 patients over 65 years of age are presented.
2. Forty-seven abdominal and 92 vaginal operations are included, with an over-all mortality of 6.5 per cent.
3. A variety of anesthetics was employed, with serious difficulty in two cases.
4. There were few postoperative complications, although no special measures in postoperative care were taken.
5. Most of the postoperative deaths occurred in patients with malignant disease, and the mortality was high in patients over 80.
6. Vaginal and abdominal surgery may be carried out in elderly gynecological patients with a minimum of risk and postoperative complication, provided care is exercised in medical evaluation, anesthesia, and operative technique.
7. Conservatism is urged in patients of extreme age, and in consideration of radical surgery in the aged patient.

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## EARLY DIAGNOSIS OF CANCER OF THE CERVIX

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SOME decades ago we considered a cancer of the cervix as an early one when the growth was limited to the cervix, not yet invading the parametria or the vagina. These ideas are superseded by the knowledge we have nowadays about the development of cervical cancer and by the various methods of detecting the pathologic condition.

There is no cancer of the human body which is so well known from its inception as that of the cervix. This is easy to understand because it can be seen, palpated, and observed. Only cancer of the skin would offer the same opportunities for observation, but it seems that the chance has not been used by the dermatologists. So cancer of the cervix became a test object for our studies on the development of cancer. It may be stated, however, that cancer of every organ has its own rules for development so we cannot apply our knowledge of cervical cancer indiscriminately to cancer of other organs. Research work on the development of cervical cancer started for very practical reasons. The results of our therapy were very poor and two ways were tried to improve it. On the one hand treatment was made more and more radical up to the exenteration of Brunschwig and the ultraradical irradiation advised by Kepp. But the results *must* be relatively bad if the cancer is far progressed and the lymph nodes are invaded. Therefore, research work turned to the other side of the problem, that is, early diagnosis. The slogan we are always propagating when talking to lay people is: "Go to the doctor when you feel the first symptom, then the cancer is in such an early stage that it can be cured with the maximal probability." But as we know very well, it is not always like that. Even if the patient goes on the very first day to consult her doctor the cancer might be quite advanced, with a bad prognosis. The aim was, therefore, to detect the cancers before they produce symptoms, i.e., to get them in the preclinical stage. This expression may be used as such, but I think it is not apt for a scientific classification. Held found that in his preinvasive cancers 39 per cent showed some slight bleeding but on the other hand there may be some early invasive cancers which present no symptoms. The ideal would be—if we cannot prevent the cancer—to detect it at least in a stage where it does not yet infiltrate the subjacent connective tissue, i.e., in the preinvasive stage. The invasion of the fibrous tissue is of great importance because, as long as the cancer is limited to the epithelium, it is, as it were, a harmless anomaly of the epithelium and not a killing disease. The step from Stage 0 to Stage I (following the international nomenclature) is the most important one in the development of the new growth because as long as the cancer is

intraepithelial it has no intimate contact with the blood vessels and the lymphatics and therefore can never produce metastases. This has to be considered also in the employment of therapy.

As everybody knows, intraepithelial cancer is not yet recognized as such by all the gynecologists and pathologists. As long as the recognition of the preinvasive stage depends on microscopic similarity or identity of the epithelium the skepticism is to be understood. Real intraepithelial cancer was discredited by those who called any anomaly of the epithelium a cancer. But we have to be as critical as possible. Only an epithelium which is morphologically absolutely *identical* with invasive cancer can be called cancerous.

Today, we do not depend only on morphology because we have other proofs that intraepithelial cancer is a real cancer. Glatthaar showed the absolutely identical behavior in culture tissue. Limburg and Uhlmann found that the anaerobic glycolysis was increased identically in the Warburg test with preinvasive and invasive cancer. Foraker, to show the hyperchromatism of cancerous cells with fluorescent light microscopy, found the same absorption with invasive and preinvasive cancer, while the metaplastic cells showed a similar absorption as that of normal epithelium. Are not these proofs enough to show us the identity of preinvasive and invasive cancer?

Even the name of intraepithelial cancer is not universally accepted. Dozens of names have been nominated. In the United States it is mostly called "cancer in situ." We prefer the word "preinvasive" (chosen by Schiller) because we think it is important to say that sooner or later the intraepithelial cancer *must* infiltrate the underlying tissue. If that were not so, we would not be entitled to call it a cancer because of the absence of deleterious effects on the host. The name, however, is the least important thing in this question.

Although we cannot discuss the whole problem of preinvasive cancer here, a few words have to be said about it. I cannot understand how anyone can deny the existence of preinvasive cancer. Cancer is an epithelial new growth and therefore it *must* start in the epithelium. Whether it grows afterward, sooner or later, into the depth is another question. After all, we know now that some cancers stay for a long time on the surface (Galvin, Jones and Te Linde), others grow fairly soon into the connective tissues (demonstrated with excellent pictures by Schiller). In the long evolution of cancer, from the first cell to the death of the host, the time that it is clinically visible seems to be of a relatively short duration. This is one more reason to look at the preinvasive stage. Lately the term "microcancer" has been used as advised by Mestwerdt. I think it should not be used at all. A microcarcinoma is a very small cancer with infiltration into the connective tissue. It is therefore nothing else than a Stage I. But how should we set limits? If it is a microcancer with a bud of 2 mm, is it still one with 3 mm.? As a matter of principle, I am against this term. From the practical standpoint, too, it is a dangerous expression because, as the literature shows, many people confuse it with preinvasive cancer, although the microcarcinoma is a fully developed cancer with the possibility

of metastases. It has to be emphasized that preinvasive cancer—the Stage 0 (J. H. Müller)—is strictly limited to the epithelium as all the various names indicate. What confusion has already been created is shown by the proposal of Gricouroff to distinguish between a “real” Stage 0 and an invasive form where the parametrium is already infiltrated and which should better belong to Stage I! I do not know either whether there is some advantage to creating a new stage: minus I (Moricard), which means to call something a cancer which is definitely not one.

As there is no doubt that every cancer must pass once in its development the Stage 0, it is quite another question whether we are able to diagnose it. Undoubtedly the diagnosis which cannot depend any longer on the destructive quality of the new growth is much more difficult.

Which methods can we use for diagnosing a cervical cancer? We can use: (1) the bimanual examination, (2) the examination with the speculum, (3) Schiller's iodine test, (4) cytology (a) the Papanicolaou test, (b) phase contrast microscopy, and (c) the Cusmano test, (5) colposcopy (Hinselmann), (6) colpomicroscopy (Antoine and Grünberger), (7) biopsy.

There is not much to be said about the old routine methods of bimanual and speculum examination. Of the latter one word may be said, that if correctly and exactly done it may show us many cancers of the beginning Stage I. But it must be more than a short glance at the cervix.

Schiller's iodine test is widely known, but the evaluation is different. It does not show cancerous epithelium but only an abnormal one, as Schiller always emphasized. Therefore, it is excellent for screening. If the cervix stains a dark brown one may be sure that there is no cancer. Whitish spots may be and may not be a cancer. Usually not. Here some other examinations have to be undertaken to get the proper diagnosis. The great advantage of Schiller's test is that it is very handy and may be used by every practitioner.

#### *Cytology.—*

*A. Papanicolaou:* About the Papanicolaou test I would not like to say much because it would be like “bringing owls to Athens” to discuss that method in detail in the United States. It is strange, however, that there are always people who emphasize that it is only a screening method. They should ask Papanicolaou himself; he never said anything else. Another objection is that the method needs too many workers and too much money. That may be true but should progress be turned back because of that? The best proof of the practicality of the method is the fact that it is used in thousands of clinics all over the world. There are other names which are connected with the development of the technique, such as Traut and Ayre. The latter gave the well-known definitions of precancerous, near cancerous, preinvasive, and invasive cells. I do not dare to judge whether such differentiations are necessary. Sometimes a too fine differentiation blurs the view of the final trend. But on one point I cannot agree with Ayre: that there is a difference in the cells between invasive and preinvasive cancer. If that were so it would be fresh justification for men not to acknowledge the preinvasive stage—that a cancer in situ is not a cancer. When we look at a slide, everyone will agree that we can speak of a preinvasive cancer only when the picture is absolutely identical with that of a fully developed cancer. Why should the picture in the smear be different? It may be different because of the different type of the cancer but not because of the different development. Of the same opinion are Zinser and Roth.

**B. Phase contrast method:** The second type of cytology is in its infancy. There are some who consider it superior to the original Papanicolaou technique. Theoretically, that could be understood because there is no doubt that we can see more details in the fresh, not fixed cell. But most competent people do not find it more advantageous than the previously mentioned method. We, at our clinic, have no great experience with it and cannot, therefore, judge of its value.

**C. A third method, the Cusmano test:** On crushed cells, this has the advantage of showing the structure of the nuclei better, but, as we do not see the protoplasm, we miss being able to judge of the plasma-nucleus relation. We have no experience with this method in our clinic.

**Colposcopy.**—This method created by Hinselmann in 1924 is widely used in Germany, Switzerland, and Austria in Europe, much used in South America, scarcely used in France, and is hardly used at all in the United States and Great Britain. For someone who uses the method as a routine, as we have done for many years, this fact is hard to understand. A priori it is to be understood that one is sure to see more with a tenfold magnification than with the naked eye. In reality the instrument is nothing more than a sort of field glass. The method is neither costly nor time consuming. But of course it has to be learned. And that might be the difficulty. The instrument alone, not handled by an expert, is worthless. What can we obtain from its use? If we look at the cervix, even with the naked eye we can detect cancers which can be only *seen*, but not *palpated*, mostly early ones. If we look with the magnifying glass of the colposcope we can see, of course, still smaller lesions. The cancerous tissue gives mostly a typical picture, different from that of an ectopic columnar epithelium or of a healing erosion. We see in some cases changes in the epithelium which we know are often found with a very early cancer. So Hinselmann's idea was to use the instrument to detect otherwise unseen carcinomas. And that is possible in a great number of cases. I think that there is another great advantage. Everybody finds now and then cases where some lesions on the cervix are seen but where it is not possible to say whether they are serious. In most cases by looking through the colposcope we see that the lesion is nothing but a simple papillary erosion or some other harmless abnormality. So you avoid an unnecessary biopsy. On the other hand, *if* we have to do one, the colposcope shows in an excellent way *where* to do it. We call it the "selective" ("gezielte") biopsy. Of course this is of no importance for somebody who always makes a ring biopsy, but if we do only a punch biopsy the colposcope is of great value. We find in the literature plenty of records where the biopsy—because made in the wrong place—gave a negative result even in the presence of a cancer. I am convinced that if colposcopy could be started in the United States with well-trained men it would find as many friends as in Europe. An excellent atlas in two volumes by Ganse and another by Mestwerdt are of great help to anybody who wants to become acquainted with colposcopy.

**Colpomicroscopy** (Antoine and Grünberger).—The idea of this technique is similar to that of colposcopy, only it leads a bit further. As said earlier, the colposcope sometimes gives the diagnosis of cancer, usually only a suspicion. Therefore it was an old aim of this method to use higher-powered lenses. But if we use a magnification of more than 20 $\times$ —the routine one is 10 $\times$ —it is very difficult to see enough because the depth of focus is minimal. Therefore these trials have been dropped. It would be necessary to use a real microscope. The idea was first taken up by Pick in the thirties. But with the technical possibilities at that time it was impossible to get satisfactory results.

I knew the work of Pick and the idea came again into my mind after having heard and seen the excellent results of Vonwiller (Rheinau, Switzer-



land) who is the leading man in the use of surface microscopy in biology, a method which is commonly used in technical fields and mineralogy. The main point was to work with incidental light. At the beginning it seemed to be impossible to produce an instrument which could be used for gynecological purposes. But finally, in cooperation with my co-worker, Grünberger, and the optical plant Reichert (Vienna), we succeeded. The instrument is an ordinary microscope and the optical part is similar to a simple microscopic tube. It is, however, not a very high-powered instrument. Magnification is at the maximum 210 $\times$ . The main difference between this and a normal microscope consists in the light which comes through the microscopic tube in a cylindrical canal around the optical system. A second important point was to get the cervix at a fixed distance from the instrument. If we do not fix it, it will move with the respiration and the pulsation of the uterine vessels. We achieved this by using a shielding tube which covers the microscope and is fixed to it. During the examination it is pressed to the cervical surface. With that the basic distance to the object is given and one manipulates the micrometer screw just as in an ordinary microscope. The field of view you get with the instrument is about 1 square millimeter. But we have to observe the whole surface of the cervix. This difficulty was the hardest to overcome. With two screws we move the protecting tube, with it the cervix, and this covers an area of about 65 square millimeters. If the cervix is not too big and/or the external os not too wide we see the epithelium around the os in its entirety. If the conditions are not so favorable we put the instrument, after having surveyed one area, to another place until we see the total area.

One prerequisite for working with this method we have not mentioned yet. We would not see anything on a cervix in its natural state. The cells and usually the nuclei are visible only when they have been stained. For that purpose we use hematoxylin as a routine. It takes about four minutes (with a soaked swab put on the cervix) to get a good staining. If we want to get a quick staining we use Pontamine Sky Blue (Du Pont). With this the staining lasts a few seconds. The picture we see is very similar to a microscopic slide of a tangential section. The different pathological conditions show different pictures (Figs. 1 and 2). The one shows the regular pattern of the normal squamous epithelium. The cells are nearly identical. The other gives the picture of a cancerous epithelium. The same qualities of the malignant epithelium which we call typical in an ordinary slide and in cytology are to be seen. What gives most certainty to the diagnosis is the marked polymorphism and polychromatism, so that we can say sometimes just from the surface microscopy that it is a cancer. This, however, is not so in every case. As we know, inflammatory conditions very often imitate cancerous epithelium because of the irregularity in the epithelial pattern. If we want to place colpomicroscopy in a category with the known adjuncts to diagnosis, we can put it between histology and cytology. We depend on *less* critical symptoms than histology because we do not see deeper layers of the epithelium and can of course not see the extension toward the connective tissue; we see *more* than the cytologist because we see the cells in situ in connection with each other. Last but not least, colpomicroscopy is the only microscopic method which enables us to see the *living* tissue and to see it repeatedly at different times. That is the position of colpomicroscopy in the different methods of diagnosing an early cancer.

**Biopsy.**—This method is considered the most dependable; some people think it an infallible one. We said before that we can easily get a wrong diagnosis if we do the biopsy on the wrong spot. But even if we do it on the proper spot and in the correct extent it is sometimes—rarely of course—hard

to make an exact diagnosis because our knowledge in judging microscopic slides has its limits. But there is no doubt that, supposing the technique is correct, biopsy is superior to all the other methods. Used as the only method it is necessary to make a ring biopsy which goes deep into the cervical canal. If we do not follow this technique the aid of one or more of the other methods would be necessary. As there are some cervical cancers which do not show any abnormality to the naked eye it would be necessary to make a biopsy in *every* gynecological case. Nobody does that and, therefore, the other methods have their great value. Biopsy is a small operation and cannot be considered in the same class as the other methods.

Fig. 1.

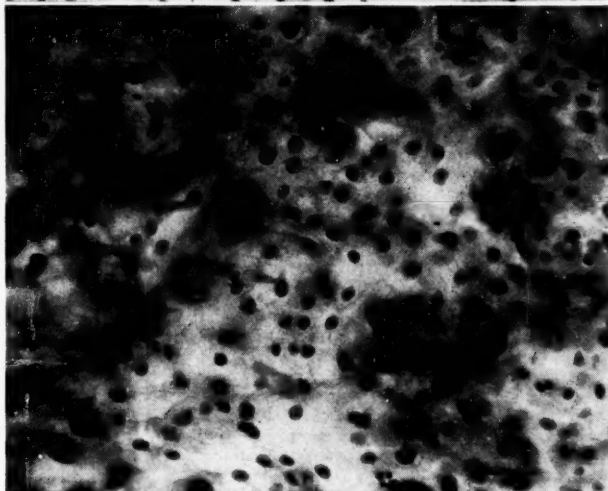
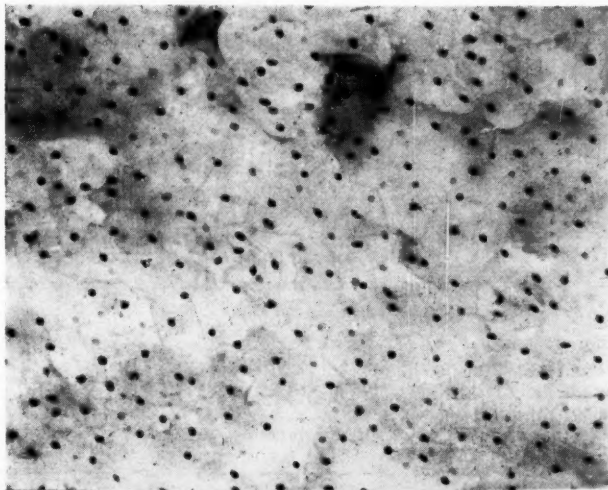


Fig. 2.

Fig. 1.—Normal epithelium of the cervix. ( $\times 200$ .)

Fig. 2.—Cancerous epithelium of the cervix. ( $\times 200$ .)

One question which arises frequently is: Which method is the best? There are some really enthusiastic idealists who believe that one method is

far superior to the others. I do not believe this. Every method has its advantages and disadvantages. Of course everyone gets the best results with the method he is used to and which he likes most. This latter is a very important factor. No one can say that any of the mentioned methods has no failures in either the positive or the negative sense. Negative errors are, of course, the more dangerous. I will give our results to illustrate this.

We use at our clinic all the methods described. Every patient accepted in the clinic gets a cytological and Schiller's test and is colposcoped. Not every patient got till now a colpomicroscopy. Any patient showing suspicious findings by any method gets a biopsy.

First, the results of our colposcopic examinations before we used cytology and colpomicroscopy: We found (Kodolitsch) in 2,953 cases 18 with the colposcope only, that is 0.6 per cent. Grünberger, one of my co-workers, found at the clinic out of 50 cases of histologically proved cancers of the cervix, 15 that were macroscopically not suspicious. The way 15 cancers were detected is shown in Table I.

TABLE I. METHODS BY WHICH 15 CASES OF EVENTUALLY PROVED CANCER WERE DETECTED IN PATIENTS WITH CLINICALLY NONSUSPICIOUS CERVICES

Cytology	2
Colposcopy	3
Colpomicroscopy	2
Cytology + colposcopy	-
Cytology + colpomicroscopy	3
Colposcopy + colpomicroscopy	2
Cytology + colposcopy + colpomicroscopy	1
Not diagnosed	2

A résumé shows that the cancer was found by cytology alone or with some other tests in 6, by colposcopy in 6 and by colpomicroscopy in 8 cases. I would not dare to say with such a small series that colpomicroscopy is superior. But it shows that we cannot say—as many people do—that you should stick to one method only and that this is sufficient. The table suggests that sometimes one and sometimes another method is superior. And it shows more: that sometimes all the methods can fail once. Therefore, our conclusions are that the different methods are not rivals and cannot substitute for each other but the more methods used the better the results will be. No one of the present methods is ideal and we still wait for better ones. In any suspicious case biopsy has to be practiced.

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## DETECTION AND DIAGNOSIS OF CARCINOMA OF THE ENDOMETRIUM BY VAGINAL AND ENDOMETRIAL SMEARS

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SINCE the pioneer works of G. N. Papanicolaou<sup>18, 19</sup> it has been known that neoplastic cells might be found in the vaginal smears during the evolution of endometrial cancers. However, most of the authors who investigated the cytological diagnosis of genital cancer have pointed out the striking difference between the accuracy of the detection of cervical cancer and the relatively high percentage of mistakes in cancers of the fundus.

Graham<sup>10</sup> reports that, on the basis of vaginal smears, 92 cancers of the fundus out of 133 were accurately diagnosed, which means an error of 30.8 per cent. Ayre<sup>1</sup> has observed 22 per cent of mistakes in a series of 31 cases.

This has been attributed to several reasons. First, lack of exfoliation of endometrial cells, which do not come down continuously through the cervix, especially in postmenopausal women when stenosis of the cervical canal may prevent the flow of secretions from the uterine cavity to the vagina, and second, the necrosis and degeneration of cells collected in the vagina, which can make the cytological recognition of neoplastic cells very difficult.

Furthermore, it has been emphasized that the cytological diagnosis, less accurate owing to the histological structure and the situation of the neoplasm, has a limited importance in cancer of the fundus. This cancer occurs mainly between 50 and 60 years of age and causes postmenopausal bleeding, which rapidly draws the attention of the patient and of the physician, leading to a curettage which confirms the diagnosis. The value of the smears as a method of detection in asymptomatic patients would, therefore, be much smaller in endometrial than in cervical carcinoma.

We have tried, on the basis of our own experience, to assess the accuracy of exfoliation cytology in the diagnosis of endometrial cancer.

Between Oct. 1, 1949, and Jan. 1, 1953, 8,525 patients of an outpatient gynecological clinic have been screened.

On the first examination, both a vaginal and a cervical smear were made. The slides were fixed in alcohol-ether and stained by the Papanicolaou technique. The smears were always repeated when the report of the first investigation was positive or suspicious or when, the first report being negative, the symptoms given by the patient led to a suspicion of cancer of the fundus. An endometrial aspiration was always made when the smears had to be repeated.

Sixty-three cancers of the endometrium were found, 13 in premenopausal patients and 50 in postmenopausal patients. Nearly all the premenopausal women were between 45 and 50 years of age. The youngest patient was 40 years old.

*False Positive Diagnosis.*—

We have included in this group, besides the cases in which no cancer was found in the operative specimen, the few cases where trace of the patient was lost following a positive smear and where no curettage or operation was performed.

The Papanicolaou classification has been used for our reports:

Type III, questionable malignancy.

Type IV, few malignant cells present.

Type V, many malignant cells present.

In patients presenting smears of Type IV or V, the results are shown in Table I.

TABLE I

NO. OF SMEARS		NO. OF CANCERS	PERCENTAGE OF ACCURACY
First smear	26	22	85
Second smear	37	33	90

In patients presenting Type III smears, the results are shown in Table II.

TABLE II

NO. OF SMEARS		NO. OF CANCERS	PERCENTAGE OF ACCURACY
First smear	42	25	60
Second smear	28	24	85

In 6 cases, endometrial cancers desquamating undifferentiated cells were mistaken for squamous-cell cancers of the cervix.

It is essential to be extremely careful before accepting a false positive when several smears of Types IV and V have been observed. The cytological examination may detect a very small cancer which can be recognized only by a thorough examination of the operative specimen.

*False Negative Diagnosis.*—

The percentage of false negative reports is obviously more difficult to assess accurately, since it is evident that in asymptomatic patients the smears were not repeated when the report was negative.

We have mainly been able to assess the false negatives in patients who had metrorrhagias and who were submitted to other procedures, curettage and operation.

In the 63 cancers of the endometrium observed, we had a relatively high percentage of false negative reports on the first smear (Table III).

TABLE III

	NO. OF CASES	
Impossible to type	10	16 cases, 25% of false negatives
Type I	2	
Type II	4	
Type III	25	
Type IV	22	
Type V	0	

On the basis of the second smear, the percentage is shown in Table IV.

TABLE IV

	NO. OF CASES
Impossible to type	0
Type I	2
Type II	4
Type III	24
Type IV	31
Type V	2

At least 6 cases were misdiagnosed after two smears.

Most of the mistakes observed on the basis of the first smears arose from the scarcity of cells on the slide; 10 smears could not be typed.

From our experience, we may come to the conclusion that when two smears of Type IV or V were reported on the same patient, the probability of the existence of a cancer of the fundus was 0.95 per cent. In the case of two Type III smears, this probability was 0.85 per cent. Obviously, a negative report does not rule out the possibility of the existence of a malignancy. Persistent bleeding or leukorrhea, especially when postmenopausal, must be followed up by a dilatation of the cervix and curettage, even if the smears are repeatedly negative.

We must emphasize the difficulties in the cytological diagnosis of cancer of the fundus. It can be carried out only by a very highly trained cytologist with great experience in the abnormal aspects of endometrial cells. The recognition of neoplastic cells is very often difficult, owing to their scarcity on the slide, their frequent degeneration, and the presence of blood and inflammatory cells. The diagnosis is especially difficult in premenopausal women, where normal or hyperplastic endometrium may shed altered cells which can be considered as malignant cells and, conversely, neoplastic cells may be misdiagnosed among normally desquamated endometrial cells.

The first condition then for the use of cytological methods in the diagnosis of cancer of the endometrium is the cooperation of a very experienced cytologist. If that condition is not fulfilled, and in France at least there are very few well-trained cytologists, it is certainly much safer not to use this technique.

However, our own experience leads us to the following conclusions:

The smear can be a useful method of *detection* of endometrial cancers in asymptomatic patients, and especially in postmenopausal women. At least 9 of our cases of endometrial cancer have been detected by smears in patients who consulted us for quite different gynecological conditions.

In *postmenopausal women who present metrorrhagias*, if Type IV or V smears are repeatedly found, we think that hysterectomy can be performed without a curettage. It seems to us that the degree of accuracy of the cytological diagnosis can be favorably compared with the reliability of the curettage, without its drawbacks.

If the smears are negative or only suspicious, a curettage should be performed before any major surgery.

In *premenopausal women* the mistakes in the cytological study seem to be more frequent, especially in the cases of hyperplastic endometrium. The curet-

tage is more easily performed, less dangerous, and no major operation should be undertaken without the results of the pathologic study of uterine scrapings.

*Estrogenic Vaginal Picture in Postmenopausal Women With Cancer of the Endometrium.—*

We have been struck by the frequency of a high karyopyknotic index\* in vaginal smears of many postmenopausal women with cancer of the fundus.

To appreciate the frequency of this condition, we have compared the respective values of the karyopyknotic index in two groups of patients: postmenopausal women without cancer, and not submitted to estrogenic treatment, and postmenopausal women, under the same conditions, who have a cancer of the endometrium (Tables V and VI).

TABLE V. POSTMENOPAUSAL WOMEN WITHOUT CANCER: 89 PATIENTS

Complete atrophy	37 or 41.5%	} 96.5%
1 to 30% of pyknosis	49 or 55%	
30 to 60% of pyknosis	3 or 3.5%	
More than 60%	0	

TABLE VI. POSTMENOPAUSAL WOMEN WITH CANCER: 37 PATIENTS

Complete atrophy	8 or 21%	} 35%
1 to 30% of pyknosis	5 or 13.5%	
30 to 60% of pyknosis	10 or 27%	} 65%
More than 60%	14 or 38%	

We have carefully eliminated any possibility of absorption of estrogenic preparations. The use and abuse of this treatment has been so widespread that we had to be very careful in the selection of our patients.

We must point out that in some postmenopausal women, estrogenic treatment induced bleeding in a latent pre-existing cancer, which has been considered as withdrawal bleeding. The correct diagnosis was made by cytology.

The difference between these two series is very striking. If it is admitted that a karyopyknotic index lower than 30 per cent is the sign of a very low estrogenic production, we see that this condition could be pointed out in 96.5 per cent of postmenopausal women without cancer against 35 per cent with cancer. Among these latter, 38 per cent had a karyopyknotic index higher than 60 per cent, showing a high and continuous estrogenic production.

What is the real significance of this fact? It is still too early to give an entirely satisfactory explanation.

We can assume that this high karyopyknotic index is the consequence of the production of a relatively high amount of estrogenic hormone in the postmenopausal patient. Where does this hormone come from? It seems very likely that the ovary is the source of this substance. When the ovaries are removed in a cancerous postmenopausal patient with a high karyopyknotic

\*The karyopyknotic index is the percentage of cells whose nuclei have undergone pyknosis. It seems to give a better evaluation of estrogenic activity than the cornification index. According to Pundel, it fluctuates between 35 per cent and 70 per cent in the menstrual cycle. Around the menopause, its average value is 45 per cent, in early menopause 10 per cent, and, in late menopause, around 0.



index, the vaginal stimulation usually disappears. However, the number of such cases we have been able to follow is still too small to draw definite conclusions on this point.

The suprarenal cortex might eventually produce estrogenic hormone in the postmenopausal patient which could stimulate the vagina.

In any case, our findings are strengthening the long-known observations of the frequent coexistence of cancer of the endometrium with the signs of an estrogenic hyperstimulation. It has been shown that in the past history of these patients sterility, persistent menorrhagias, late menopause, sometimes even induced by x-rays, were very frequently reported, suggesting an excess of stimulation by estrogenic hormones without rhythmical production of corpus luteum hormone (Corscaden,<sup>4</sup> Gusberg,<sup>11</sup> Randall,<sup>21, 22</sup> Herrell<sup>13</sup>).

Very often in these postmenopausal patients no atrophy of the vulva, labia, and vagina exists.

Endometrial cancer is often observed in patients with cystic glandular hyperplasia. More than 30 years ago, R. Meyer pointed out that no sharp division could be traced between these two conditions.

Many authors have insisted upon this coexistence (Taylor,<sup>23</sup> Novak and Yue,<sup>17</sup> etc.). Estrogen-producing tumors of the ovaries are frequently associated with cancer of the fundus; according to Dockerty and Mussey<sup>6</sup> and Ingram and Novak,<sup>14</sup> in 15 to 20 per cent of the cases. A hyperplasia of stromal cells of the ovaries which might produce estrogens has been found in postmenopausal cancerous women (Woll, Hertig, Smith,<sup>28</sup> and Johnson, Novak and Mohler<sup>16</sup>).

However, if this estrogenic hyperstimulation is often observed, it is not a *sine qua non* condition.

In 20 per cent of the patients in our own series, completely atrophic smears have been reported. This atrophy has sometimes led to technical difficulties when carrying out endometrial aspirations and curettages. But in the great majority of cases, a definite production of estrogenic hormone could be found. The finding of a high karyopyknotic index in a postmenopausal woman without neoplastic cells has led us to repeat the smears and sometimes to find an unsuspected endometrial cancer.

On the basis of our findings, we suggest that patients whose past history of menstrual irregularities, persistent menorrhagias, or late menopause suggests an excess of estrogenic production should be submitted each year to a cytological investigation in order to detect an early-stage carcinoma.

### Summary

Endometrial carcinoma can be diagnosed with satisfactory accuracy through the use of cytological methods. Endometrial aspiration associated with vaginal smears gives a lower percentage of false negative reports.

The cytological diagnosis of endometrial cancer is more difficult than the recognition of squamous-cell cancer of the cervix, especially in premenopausal patients. It can be carried out only by well-trained cytologists with considerable experience.

In postmenopausal bleeding, a repeatedly positive smear is strongly suggestive of endometrial cancer.

As a method of detection of fundus carcinoma in asymptomatic patients, vaginal and endometrial smears are certainly very valuable, especially in patients whose past history suggests a lengthy duration of hyperestrogenic stimulation.

In postmenopausal patients with endometrial cancer, a high karyopyknotic index may be found in vaginal smears, indicating a definite production of estrogenic hormones. This condition has been reported in more than 65 per cent of our patients, suggesting that, in the majority of the cases, fundus carcinoma arises in an endometrium which has been stimulated more or less continuously by estrogenic hormones.

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## THOUGHTS ON FORTY YEARS OF RADIATION TREATMENT OF CARCINOMA OF THE UTERINE CERVIX

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*(From the Radiumhemmet)*

IT IS a great pleasure to contribute to this volume in honor of Dr. George W. Kosmak and to report on a subject which has attracted much attention during the 30 years in which Dr. Kosmak has acted as the editor of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

In the first decade of the present century surgery was the only method of treatment by which an apparent cure in cancer of the uterine cervix could be obtained. Characteristic of this period were the great efforts to improve surgical technique, to reduce the operative risk, and to extend surgery to embrace cases where the carcinoma was no longer confined to the cervix, the so-called borderline cases. Wertheim and Schauta were the great pioneers of this period.

In spite of all efforts, the radical operation was a dangerous procedure in those days and the results obtained were not up to expectations. The primary operative mortality was high, averaging 20 per cent and only occasionally less than 10 per cent. The absolute 5 year recovery rate was generally less than 20 per cent, only occasionally reaching 25 per cent. The number of advanced cases in which a radical removal of the growth was out of the question averaged 40 to 50 per cent of the total number examined. Figures more favorable than the averages mentioned above were occasionally presented, though usually relating to occasional and relatively small series of cases. As a rule less favorable results were obtained even by expert gynecological surgeons.

It is not to be wondered at that the introduction of radiotherapy under the then prevailing circumstances raised unduly high expectations. For the first time in history a means seemed to be available for selective treatment of cancer.

This was indicated by a rapidly increasing number of cases where the growth had apparently entirely disappeared and conditions had been restored to normal following radiotherapy. The marked palliative effect of radiotherapy even in advanced and hopeless cases was rapidly acknowledged.

In less than a decade it became obvious that by radiotherapy an over-all 5 year apparent recovery rate could be obtained which compared favorably with that obtained by surgery, in spite of the fact that the radiotherapeutic series contained a higher proportion of cases less favorable from a prognostic point of view than did the surgical series.

During the same period it was also gradually realized that radiotherapy was a dangerous weapon which had to be carefully administered. Careless irradiation was often followed by severe injuries to the patient.

From about 1920 and subsequent years the most important problem under discussion was whether or not it would be justifiable to extend radiotherapy to the early, operable cases.

I should like to quote the following which I<sup>1</sup> wrote on this subject in 1918:

Because of the results obtained with radiotherapy in a series of inoperable cases of carcinoma of the uterine cervix, treated at the Radiumhemmet in Stockholm, we are convinced that not only is radiological treatment of operable cases justifiable but we consider it highly desirable that it should be tried on a large scale. . . . We do not yet know to what extent the primary radiotherapeutic results will prove to be permanent. Only when such knowledge is available will it be possible to judge whether or not surgery will be entirely superseded by radiotherapy in the treatment of cervical carcinoma.

Today the situation is different. The justification of radiological treatment in early cases of carcinoma of the cervix is no longer in question. Both the absolute apparent 5 year recovery rate and the stage rates obtainable by radiotherapy are considerably higher than those obtained during the preceding surgical era.

The 5 year apparent recovery rates obtained at the Radiumhemmet in a series of 1,548 cases examined with a view to treatment in 1942 to and including 1946 are as follows:

Absolute apparent recovery rate	42.2%
Apparent recovery rate in:	
Stage I (191 patients)	69.1%
Stage II (801 patients)	49.8%
Stage III (387 patients)	28.4%
Stage IV (107 patients)	11.2%
Stages I-IV (1,486 patients)	43.9%

The figures relate to unselected material, since the Radiumhemmet is responsible for the treatment of all cases of carcinoma of the cervix within a geographically defined area. Similar results are obtained at a number of other institutions.

In addition, adequate radiotherapy can be administered without subsequent serious injury. In the Radiumhemmet series of 2,756 patients treated from 1936 to 1945, there were 0.9 per cent serious injuries to the bladder and 1.1 per cent to the rectum, the total number of vesicovaginal fistulas being 0.25 per cent and of rectovaginal fistulas 0.3 per cent.

The problem today is whether or not the recent tendency to substitute surgery for radiotherapy in apparently early, operable cases is justifiable. The reasons given for extended use of surgery are (1) the fact that radiotherapy fails in 30 to 40 per cent of these cases, (2) the fact that modern surgery offers great facilities for a considerable reduction of the earlier primary operative mortality, and (3) the hope that there might be a possibility of im-



proving the final results by applying primary surgery to the cases where radiotherapy will fail. The point at issue is to find out if there is such a possibility.

Two reasons for radiotherapeutic failure are generally mentioned: first, that there are cases which do not respond to radiotherapy (the so-called "radioresistant cases") and, second, that node metastases cannot be controlled by radiotherapy. So far efforts to distinguish "radioresistant cases" prior to treatment have failed. Thus, it is at present impossible to present a series of such cases prior to radiation and, consequently, no comparison of results in such cases can be made. Ruth Graham's most interesting studies on the reaction of normal vaginal epithelial cells following radiotherapy may offer a possibility of determining the prognosis and may prove to be a contribution of revolutionary importance.

The statement frequently made that node metastases cannot be controlled by radiotherapy is not correct. There are cases with microscopically verified node metastases where a permanent recovery was obtained. It is in the nature of things that microscopic verification of lymph node metastases is only occasionally available in radiologically treated series of cases. Therefore, we do not know the proportion of cases where lymph node metastases are controlled by radiotherapy. Nor do we know if the final results obtained by surgery in these cases are superior to those obtained by radiotherapy.

Comparison is frequently made between results obtained by surgery in selected cases and those obtained by radiotherapy in Stage I. Reliable comparison of such series is impossible since series of cases selected in different ways are not comparable. Unreliable comparisons are not justifiable and should be abandoned.

The only way at present available for a correct estimation of the value of the extended use of surgery is as follows:

1. Classify all cases examined at the institution, on the basis of findings at clinical examination prior to any treatment.
2. Let the cases remain in that stage irrespective of any findings at operation or microscopic examination of removed specimens.
3. Report on all cases allotted to Stage I.
4. Compare the results obtained in all Stage I cases between institutions favoring surgery and those limiting operation to cases of radiotherapeutic failure or with local recurrence.

The 69 statements published in Vol. 8 of the *Annual Report on the Results of Treatment in Carcinoma of the Uterus* offer a possibility for such evaluation. The submitted figures do not indicate that the 5 year recovery in Stage I is better at institutions favoring primary surgery than at those practicing primary radiotherapy.

Statistically significant surgical series have not yet been presented to prove that the extended use of primary surgery is indicated at institutions where adequate radiotherapy is available. Whereas the value of radiotherapy is ascertained by statistically proved facts, conclusive evidence of the value

of primary surgery is not yet available. It seems desirable that the responsibility for the establishment of such evidence should be left to the most expert gynecological surgeons. In the meantime the extended use of surgery should not be advocated. If practiced by the average surgeon and gynecologist the final result may prove catastrophic.

In addition, the advocating of surgery may unnecessarily delay the urgently needed establishment of adequate radiotherapeutic facilities in areas where they are still lacking.

The "American operation" (Brunschwig) is of considerable importance in the treatment of patients who are suffering from pain and discomfort due to recurrence and radiation injury and in whom less radical surgery or repeated irradiation is no longer possible.

Adequate radiotherapy requires experience. The radiotherapist must know how to adapt the treatment in each individual case to local conditions—such as shape and extent of the growth and the width of the vagina—and to the general condition of the patient. He must know how to deal with complications such as anemia, salpingitis, pregnancy, and, above all, infection. In most cases the treatment technique must be varied with a view to the varying anatomical conditions and the complications mentioned before. In others the treatment planned has to be changed because of complications that arise during treatment. There is every reason to believe that individualization of treatment is to a great extent responsible for improvement of the results. Because of this I consider it important that one man should carry the entire responsibility for his patient whatever treatment is employed, whether radium, x-ray, or surgery. Divided responsibility and careful individualization are incompatible. Adequate radiotherapy requires hospitals which are equally as well equipped, well staffed, and well organized as those for surgery. Even then, good results cannot be obtained and severe injuries cannot be avoided, in surgery or in radiotherapy, unless they are practiced by men who have acquired the necessary skill and experience.

I have, more and more, become convinced that all treatment of carcinoma of the cervix should be carried out in special central institutions devoted solely to this treatment, and well equipped both for radiotherapy and surgery because of the many difficulties involved.

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## THE RADIATION TREATMENT OF CANCER OF THE UTERINE CERVIX

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I HAD the honor to report on the treatment of cancer of the uterine cervix at the International and Fourth American Congress on Obstetrics and Gynecology held in New York in May, 1950. At that time, I discussed in particular the question of operation or radiation with reference to the world literature and statistics as far as they were then available to me.

Both methods were in a comparatively settled stage of development and investigations led to the conclusion that neither operation nor radiation was to be preferred in general. The best results could be achieved by a careful selection of one or the other method for each special case or, in certain cases, by a combination of both.

Since that time, the treatment of cancer of the cervix has entered a new developmental phase more rapid than has occurred in almost any other gynecological disease. This new development was due to the new achievements of modern surgery as well as to the progress of radiation techniques and to nuclear physics. In this paper, I shall try to outline which of the recently discovered methods seem to promise success and which ought to be studied further.

The fundamental principle of directed, highly fractionated, small-volume radiation seems to have met general success in the radiation therapy of malignant tumors. This method attempts to strike the tumor tissue and conserve the surrounding normal tissues which carry the defense mechanisms. If we had the technical ability to restrict ionizing radiation to the tumor tissue alone, we should not need a biophysical selectivity of the rays. If we possessed highly selective rays, we should not need a technical method of limiting them to the tumor. Neither possibilities have been realized. We, therefore, must endeavor to reach our goal by both means, that is by technical and by biophysical methods. The question arises whether the ordinary x-rays will be adequate in the future, or whether we shall have to turn to supervoltage therapy with high velocity electrons and ultrahard x-rays or to radioactive isotopes.

The ordinary x-rays of 200 to 400 kv. using stationary fields appear to have exhausted their possibilities. The highly fractionated doses and the principle of small-volume radiation constitute the most recent great advances. By both methods success has been considerably increased. Now, in addition, a long-sought objective has been reached, that is, the so-called motion therapy which has proved very useful in the treatment of cervical cancers. The first

experiments I saw were performed with swinging tubes, when I went from Bonn to see H. Meyer in Kiel in 1913. The technical realization of this fruitful idea took 30 years. Motion therapy is far better suited to the small-volume radiation, in so far as the conservation of the normal tissues is concerned, than is radiation of stationary fields.

We are about to evaluate the new apparatus for rotation, pendulum motion, and convergence therapy, and to include these in the clinical plan of radiation treatment. By an eccentric, complete rotation one can obtain in parametrial tumor infiltrations a dosage of 232 per cent of the superficial dose (Wachsmann-Keller), although we have to admit that this means an overdosage of the bladder and rectum. Therefore, we still prefer for the treatment of the primary tumor in cancer of the cervix the intracervical radium therapy with its very favorable distribution of dosage. For the parametria we add intravaginal radiation from inside by means of a hollow anodal tube and a percutaneous band of radiation to the pelvis from outside applied as a unilateral or bilateral eccentric pendulum radiation at an angle of 220 degrees (Kepp, Baeumer). In this way, the parametrial foci receive 180 per cent of the superficial dose while the bladder and rectum are sufficiently spared. If there are foci near the pelvic wall, that is to say, recurrent tumors after operation or radiation at the pelvic wall, a band of radiation by means of pendulum technique combined with intravaginal radiation is particularly valuable. The best size of the field for parametrial irradiation is a 4 cm. wide portal. The height depends on the expansion of the palpable tumor and may extend to 8 cm.

In Germany, the pendulum apparatus of the Siemens-Reiniger factories and the universal unit for motion radiation of C. H. F. Muller are available for producing a band of radiation by motion therapy. Since these forms of apparatus were installed in our clinic only recently, I can report only on the preliminary results. They were surprisingly successful, in particular for highly placed recurrent tumor masses in cancer of the genital organs, even when they were situated among the intestinal loops. Moreover, it is remarkable that the patients tolerate pendulum radiation far better than the stationary field radiation since the simultaneous radiation of normal tissue is much less when adequate tumor doses are being given. If the vagina is accessible, we combine the band producing motion therapy with the intravaginal anodal tube irradiation, so that the tumor is taken under cross fire. The skin dose can be kept so low (70 to 85 r superficial dose for each treatment) that no considerable skin reactions occur. This corresponds to a focal dose of 150 r for each treatment. Without doubt, the simultaneous irradiation of the intestines, in particular if they are fixed, represents a very considerable danger due to the high total dose of the deep radiation.

In convergence treatment, the x-ray tube is moved over a driving gear in such a manner that the roentgen focus moves in a narrow spiral over the surface of a spherical calotte while the screened-off roentgen beam remains constantly pointed toward the convergence center which is directed on the



focus. The cone of rays strikes the skin in a snail-shaped line. According to the depth of the convergence center (to 11 cm.) and to the size of the cone of beams, the respective depth dose may reach 380 per cent of the superficial dose.

We are now trying to establish by means of phantom measurements how the convergence therapy can be made useful for gynecological radiation treatment and for cancer of the cervix in particular, in order to evaluate the various forms of motion radiation. We consider ourselves entirely justified in stating that the percutaneous motion therapy producing a band of radiation as an addition to the intracervical radium and the intravaginal x-ray treatment will improve the therapeutic results in cervical cancer as well as in other malignant growths.

All the aforementioned methods of motion radiation and the apparatus constructed for them offer a favorable spatial distribution for the ordinary x-rays to a degree never reached before. The question arises whether we shall achieve even more with the new kinds of rays in the supervoltage therapy, that is with high velocity electrons and with ultrahard x-rays or with artificial radioactive substances. This question has certainly to be answered in the affirmative as far as the electrons of high velocity and tumors near the surface are concerned. It is easy to regulate the depth of penetration of high velocity electrons by means of the voltage applied to the generator. Beneath the point of intended maximum dosage, the dose of the beta rays is suddenly diminished which is very favorable for the normal tissue below the tumor, where of course x-rays have no such sharp demarcation in their effective strength. We have made use of this physical property of the electrons of high velocity in the treatment of vulvar cancers, for which we achieved surprisingly good results by means of a 6,000,000 volt laboratory generator in the Second Physical Institute in Gottingen (Kopfermann, Paul). These results were published by Martius, Kepp, Baeumer, Paul, Schmermund, and Schubert. For the deeper and more centrally seated tumors including the extensions of cancers of the portio, the ultrahard x-rays are more favorable from a physical standpoint. The necessary deep dosage is easily achieved. Other physical advantages of these rays include the favorable relationship between superficial and depth dosage, the independence of the depth dose from the size of the field, the clear demarcation of the cone of beams, the only slight alteration of the depth dose by bony tissue, and finally the small volume dose. A particularly favorable distribution of dosage may be obtained by developing the ultrahard x-ray radiation as motion therapy, as is done in the 15,000,000 volt generator of the Siemens-Reiniger factories. Trump and Hare, Smithers and others have shown in a convincing manner that the combination of supervoltage therapy with motion radiation constitutes the best method for the radiation treatment of deep-seated foci.

In addition to the problem of the best spatial distribution of dosage, we have to discuss whether and to what extent supervoltage therapy in contrast to the ordinary x-rays has a greater differential effect on the tumor than on normal tissues due to its different temporal and local distribution of ionization.

Without this biophysical selectivity of the rays any tumor treatment is aimless. It has always been our endeavor to increase in one way or the other the aforementioned differences in the sensitivity to rays between the tumor and the surrounding tissue.

During recent years we have concentrated our biophysical investigations on this question. It is difficult clinically and experimentally to demonstrate differences in selectivity of different kinds of rays with various ion density since the necessary condition for proof is a homogenous distribution of dosage in the tissue or in the object of experiment. In unequal distribution of dosage, the varied course of the dosage effect curve in various ion densities may produce a seeming selectivity. Various experimental investigations, as for example those on barley shoots and barley roots, *Drosophila* eggs, corneas of salamander larvae, Ehrlich cancer in mice (G. Schubert and his group), Walker cancer in rats (Hofmann and Wachsmann), fibroblasts of chicken hearts (H. Gartner), and others, allow us to assume that in all probability the high velocity electrons and the ultrahard x-rays have a higher selectivity for rapidly growing, abnormal tissues than for normal ones. An increase in this selective effect may be obtained if the total dosage of the ultrahard radiation chosen is not too high (Kepp, Müller, and Reich). Certainly we consider it promising for physical as well as for biophysical reasons to develop super-voltage therapy further.

The treatment of cancer of the cervix with artificial radioactive isotopes has also to be further investigated. R. L. Meiling (Ohio University, Columbus, Ohio) has developed and recommended a method using aluminum needles containing cobalt.<sup>60</sup> Many other similar experiments have been carried out. Radiocobalt is already much in use for therapy at short and long distances. In cancer of the cervix it has to be used, in my opinion, as a substitute for radium. It will be a financial question whether it will be preferred to radium. Also in the treatment of cancer of the cervix, injections of radioactive colloidal gold into the parametria have been tried (Hahn, Sherman-Bonebrake-Allen, J. H. Muller, and others). It is clear that many new ways are open in radiation therapy all of which are worth following until we have learned which is the best.

The surgical treatment of cancer of the cervix is also in a phase of turbulent development in view of the present general tendency of the surgeons to radicalism. In addition to the widening of the limits of surgery, special combinations of operation and irradiation are often used. The gynecological roentgenologist, Gorton of Lund, for example, radiates cancer of the cervix and generally removes the extraperitoneal lymph nodes some time later. Read, Taylor, Parson, Wilson, and Morse report on the same method. Mitra of Calcutta performs a radical Schauta-Stoeckel operation and resects the extraperitoneal lymph nodes some time later. Generally speaking, the gynecological surgeons tend to be extremely radical as to the resection of lymph nodes (Taussig, Brunschwig, Meigs, Antoine, Navratil, Nathanson, W. Schultz, W. Bickenbach, Dargent, Brenier). Personally, I continue in the time-tested procedure of removing at the Wertheim operation only nodes which seem

abnormal to palpation, in order not to deprive the patient of the natural protection of the lymph nodes and afterward apply fractionated irradiation. I intend to use this method until statistical results decide against it.

From all these facts, it is obvious that we have not arrived at an end to development in the treatment of cancer of the cervix. On the contrary, new developments have appeared and without doubt should be encouraged. The main task of the clinician is to become familiar with the new achievements of surgical techniques as well as with the physical fundamentals of radiation therapy so that he may be able to decide upon one special method and use it consistently over a certain length of time. The decision as to the best course of treatment cannot be reached by observing a single case, but only by reliable and sufficiently large numbers, although the manifold variations to be considered also present difficulties in the statistical analyses.

## THERAPY OF THE LATERAL PELVIC NODES IN CERVICAL CARCINOMA

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THE importance of adequate therapy to the lymphatics of the lateral pelvic wall in patients with carcinoma of the uterine cervix has long been acknowledged. During the decades covered by Dr. Kosmak's editorship many studies have reconfirmed this<sup>1</sup> and many techniques have been proposed to achieve control of the spreading carcinoma in the nodes of the lateral pelvis.<sup>2</sup>

Taussig<sup>3</sup> employed surgical dissection of the lateral nodes together with radiation therapy for the central lesion, a suggestion which has been made again more recently by Kimbrough.<sup>4</sup> The addition of lateral pelvic x-ray ports to provide increased side-wall dosage of irradiation has been tried but is associated with an increased incidence of spontaneous fracture of the neck of the femur.<sup>5</sup> Transvaginally placed interstitial needles<sup>6, 7</sup> are intended to increase the dosage to these nodes by placing the sources of radioactivity in the neighborhood of the lateral wall. Sherman and his co-workers<sup>8</sup> have proposed reaching this area by the paracervical injection into the tissues of colloidal suspensions of radioactive gold.

The present paper discusses another approach to this problem. In 1951 Morton and his associates<sup>9</sup> proposed the use of fine Nylon tubing as a carrier for multiple weak sources of radioactive cobalt. Such a unit constitutes a plastic and pliable "needle" which possesses unique characteristics as a container for radiation sources in interstitial therapy.<sup>10, 11</sup> This tubing can be so attenuated that it can be threaded into a surgical needle for sewing directly into the area to be treated. More recently, these Nylon "threads" with radioactive portions have become available commercially. While their application in this particular field has not been extensive, and no five-year results are available, the technical details of their use merit discussion as a potential approach to the therapy of the lateral pelvic nodes in carcinoma of the cervix.

*The Threads.*—Fine cobalt wire (0.5 mm. diameter) is cut into lengths of one-third centimeter and activated so that each such piece has a strength of 0.2 mc. These cobalt pieces, with aluminum spacers of the same size, are placed in Nylon tubing of 1.75 mm. outside diameter. When the active sections of such "threads" are placed parallel and at an interval of 1.0 cm. from each other a field is created which yields about 1,000 gamma roentgens per day to the immediate area. Since the strength of such a field results from the cross-firing of multiple sources which are individually weak, it falls off



sharply on either side of the planar zone in which the threads lie. The exceedingly weak beta ray of  $\text{Co}^{60}$  requires no other shielding than the walls of the Nylon tubing.

These threads can be so loaded that the active portion ranges between 3 and 10 cm. That portion of the tubing which is inactive can then be warmed and attenuated by stretching to the caliber of heavy retention suture (No. 5 Silk). The total length of the thread should preferably be 36 inches or more, permitting the sewing which places the threads to be carried out while the active section is completely shielded.

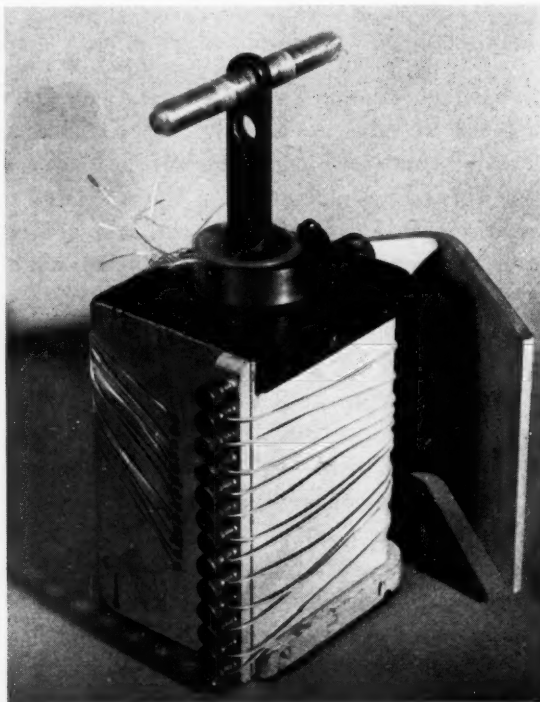


Fig. 1.—Lead block container for threads. Inactive tail of thread fastened on outside of box. Radioactive portion in individual small holes bored through block. Long inactive "leaders" gathered around spool at base of handle. Hinged door on back closes around over holes on back and inactive portions on side.

*Technique.*—With the section of Nylon thread which is active contained in the center of a heavy block of protective lead (Fig. 1), and with the inactive ends wrapped around the outside, the entire unit can be sterilized by soaking in Zephiran 1:10,000 prior to being transported to the operating room. This particular technique represents interstitial therapy which, when applied to pelvic lesions, requires a laparotomy. In contrast to techniques employing transvaginally placed needles, the viscera and vessels of the pelvis are under direct vision while the radioactive sources are being placed.

Prior to laparotomy the patients have all received external irradiation which delivers about 3,500 gamma roentgens to the midpelvic plane over a 24 day period, as well as intravaginal therapy with colpostat and tandem which adds another 6,000 gamma roentgens to the total dosage in the paracervical

region (Point A). Whether the x-ray precedes or follows the intravaginal therapy with colpostat and tandem depends in great measure on the nature of the initial lesion and the clinical findings. The laparotomy is scheduled to follow this therapy, usually within 24 or 48 hours.

At laparotomy, pelvic and general abdominal exploration are carried out, and any desired biopsies obtained. Threading the inactive length of the Nylon, the surgeon picks up small bites of lateral-wall peritoneum to anchor the threads over the area to be treated. In general, these bites of peritoneum are taken so that the thread will be anchored approximately parallel to the iliopectineal line. The next thread is similarly anchored parallel to the first, but 1 cm. lower in the pelvis. This sewing continues, using only the inactive

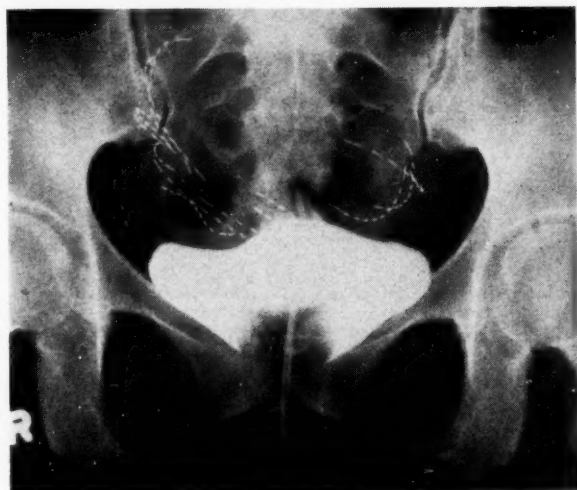


Fig. 2.—Anteroposterior view of pelvis with lateral threads in place.

portions of the thread until the area to be irradiated is fully covered. When parallel rows at 1 cm. intervals have been placed satisfactorily, the radioactive portion is drawn out of the shielding lead container until it lies over the nodal region. The ends of the threads are left long and brought out of the wound at the lower pole. The incision is then closed, with emphasis on speed rather than meticulous precision of technique. Postoperative pelvic x-rays (Figs. 2, 3, and 4) can be taken to check the thread placement.

The duration of such therapy depends on the total dosage desired at the lateral pelvic wall. Since, under the average course of therapy outlined above, the lateral pelvic wall (Point B) has received between 3,000 and 4,000 fewer gamma roentgens than has the paracervical region, and since parallel threads at 1 cm. intervals produce 1,000 gamma roentgens per 24 hours, the threads remain in place, in most cases, about 4 days. No anesthesia is necessary for the removal of the threads, and no form of secondary closure has as yet been required for the lower pole of the incision through which the threads emerge.

*Dosage Calculation.*—Threads with 7 active cobalt pieces (0.2 mc. each) and six aluminum spacers will have a 4 cm. active length. Assuming that six such threads are sewed with parallel spacing in a plane, the covered area is

4 by 5 cm., or 20 sq. cm. This field falls off rapidly at the open ends of the threads, but an area of 5 by 3 cm. receives an average dosage of 854 roentgens per day (24 hours). If two additional threads can then be sewed across the

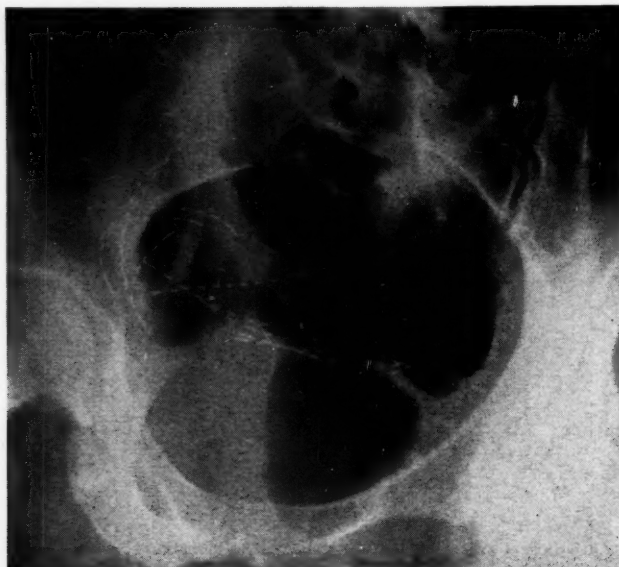


Fig. 3.—Oblique x-ray of pelvis with threads in place. Aluminum spacers do not show in film.



Fig. 4.—Oblique view of pelvis after sewing lateral wall with radioactive threads.

active ends of six initial threads at right angles to them, the field is made more uniform, and the enclosed area of 5 by 4 cm. receives 1,140 roentgens per day. This form of planar implant (parallel rows with crossing threads at right

angles over the ends of the parallel group) can usually be achieved in the pelvis without too much technical difficulty. Similarly, eight threads of 4 cm. active lengths sewed parallel with the ends crossed by additional threads will produce a field 7 by 4 cm. which receives 1,120 roentgens per 24 hours.

### Comment

The present paper is not concerned with results; an insufficient number of cases (48) have been treated with this method to make these of any significance. The present paper simply outlines one possible approach to the therapy of the lateral pelvic lymphatics. While  $\text{Co}^{60}$  lends itself well to this form of regrouping and requires minimal shielding, and while the Nylon tubing constitutes an ingenious pliable "needle" for interstitial therapy, the writer is not concerned with "selling" this particular technique. Other sources of radioactivity and other methods of applying them may well be presented with undoubted advantages.

The writer is interested, however, in "selling" a sense of dissatisfaction with half-doses. Adequate external x-radiation, plus central pelvic therapy from x-ray cone or from colpostat and tandem, delivers to the lateral pelvic nodes—one of the first major areas of bodily involvement outside the cervix itself—a dose of irradiation which is insufficient to destroy carcinoma. Dismissing a woman in such a state of half-treatment as being "treated to tolerance" is analogous to discharging a diabetic patient on one-half the required amount of insulin as a maintenance dose. The final results with this particular technique are not as important as is a continued effort to improve the therapy of the nodes of the lateral pelvic wall.

### Conclusion

Aside from the eradication of the primary growth, adequate therapy for the lymph nodes of the lateral pelvic wall is the principal challenge in the treatment of cervical carcinoma. A possible answer to this challenge is suggested and the technique is outlined for the use of the Nylon "thread" loaded with radioactive cobalt for irradiating the pelvic wall in patients with cancer of the cervix.

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## THE PITFALLS OF RADICAL PELVIC SURGERY PERFORMED FOR ADVANCED CARCINOMA OF THE CERVIX

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THE renaissance of surgery as a method of therapy in carcinoma of the cervix poses numerous questions as to its future role in the management of this disease. Time will answer some of these questions when various adequate series have been evaluated. Wertheim, Reis, and John G. Clark initiated the attack with the first radical hysterectomies. This was, of course, prior to the introduction of radium as a therapeutic means.

Now, once again, surgery supported by antibiotics, improved anesthesia, and blood replacement is called upon to salvage those patients in whom radiation has been unable to stop the advance of carcinoma. In this grim effort, mortality and morbidity statistics today are high, but the disease would certainly give inevitably fatal results with progression that a heroic surgical attempt might forestall.

Irradiation therapy is still the method of choice in the treatment of carcinoma of the cervix. Therapeutic techniques may vary but the physical principles of dose distribution are uniform. An adequate tumor dose must be delivered initially without subjecting the bowel or bladder to over 5,000 gamma roentgens. External irradiation should always be administered first, especially in exophytic lesions, to shrink the tumor and sterilize the tissues as much as possible before the trauma of the radium insertions. Radioactive isotopes such as cobalt<sup>60</sup> and gold<sup>198</sup> have not shown much promise in cancer of the cervix. The earliest detection of radiation failures is most important. By such detection, surgery can be facilitated, since procedures attempted prior to heavy radiation fibrosis are attended by much less technical difficulty. This is not meant to suggest that surgery be used routinely in combination with radiation, as in endometrial cancer, for, in cervix cancer, the fibrosclerosis can serve effectively to entrap the tumor cells. Surgery, if performed injudiciously, may serve only to spread the disease throughout the pelvis.

Presently, we must follow the irradiated patient closely, employing cytologic study and biopsy where indicated to determine whether residual disease persists. When it has been found, the patient can be subjected to whatever extensive surgical procedure is necessary to free her of disease.

Reirradiation, if sufficient time has elapsed since the previous therapy, will again arrest some tumors. Certainly mention must be made of this approach prior to any discussion of procedures that glibly deal with wet colostomies, urinary pouches, and skin ureterostomies. Reirradiation, with the ever-attendant danger to bladder and rectum, should not be considered as having failed if the patient, cured of disease, sustains vesical or rectal fistulas as an aftermath of therapy. These too can be treated surgically.

Any evaluation of the surgical hazards must first consider the selection of patients. In the main, radioresistance as determined clinically or by smear and biopsy is the chief determining factor, with, second, those patients not suitable for radiation, i.e., those who have cervix cancer complicated by other pelvic tumors (uterine or ovarian) or by marked prolapse. In the group of radioresistant lesions, certain criteria must be fulfilled prior to radical surgery. In the remaining cases, surgery, if performed at all, must be only palliative.

If the general condition of the patient will withstand such an extensive procedure, the facts are presented so the patient may accept or decline as she chooses. First, there must be no edema in either extremity due to the disease. Second, there must be no evidence of extension of disease beyond the pelvic brim. Third, kidney function must be adequate.

### **Preoperative Preparation**

Preoperative preparation must begin with careful evaluation of the urinary tract drainage structures. Uremia is the assigned cause of death in the great majority of fatal cases of cervix carcinoma. In Henriksen's series of necropsies on patients with cancer of the cervix, 58.5 per cent of nontreated patients and 49.3 per cent of treated patients died in uremia. An additional 24.3 per cent of the nontreated and 29.3 per cent of the treated patients showed ureteral compression and kidney damage.

Determination of the nonprotein nitrogen and intravenous pyelography as indicated are followed by cystoscopy for evaluation of the bladder to determine whether or not there has been early invasion as evidenced by bullous edema or fixation.

In those instances where urinary function is impaired due to occlusion of one or both ureters by disease, emergency measures such as skin ureterostomy or nephrostomy are performed and supportive therapy continued until kidney function is adequate to permit further surgery.

The construction of a urinary pouch as described by Gilchrist may be utilized and is a satisfactory means of replacing the urinary bladder. It is a formidable procedure which adds a great deal to the patient's load and had best be performed before exenteration. Re-entering the abdomen after exenteration proposes greater technical difficulty in making the cecal pouch. Wet colostomy, although difficult to manage so that the patient can be dry and free from odor, is preferable in our experience to cutaneous ureterostomy. In the latter instance, the ureteral opening tends to retract and become stenotic, and the urinary flow is uncontrollable unless catheters are used. Catheters require frequent changing and infection is as frequent in the urinary tract as when ureterosigmoidostomy is performed.

The bowel must in turn be evaluated prior to the contemplated surgery. In most instances, proctosigmoidoscopy gives sufficient knowledge of the pelvic colon and whether or not it has been invaded by the malignant process. In some cases, it may be necessary to perform barium studies to evaluate the colon adequately.

Simultaneously with these preparations, the patient's general condition is evaluated; the cardiac-pulmonary status is determined by an internist with electrocardiographic tracings, chest x-ray, blood and urine studies, as indicated in each case. Anemia is corrected with whole-blood replacement. Hydration and nutrition are maintained at optimum levels. Exenteration places a heavy demand on the cardiovascular system and the excretory mechanism of the human body. To evaluate a patient medically as to her ability to tolerate major surgery is inadequate evidence that this particular patient could withstand the added strain posed by exenteration, partial or complete. The medical consultants must build a new standard of physical fitness before approving a patient for this extensive surgery.

Seventy-two hours prior to radical extirpative surgery, the following routine is begun. The patient is placed on a low-residue diet and bowel preparation started. Terramycin (2 to 3 Gm. per 24 hours) is given to prepare bowel and bladder. Vitamin K is used in conjunction with the antibiotic which disturbs the coliform organisms. Forty-eight hours prior to surgery, purgation is started. Magnesium sulfate and castor oil given orally empty and deflate the bowel. The diet is liquid and supplementary fluids may be used to prevent electrolyte imbalance if much fluid is lost during purging. Twenty-four hours prior to surgery, enemas are given until clear. A Miller-Abbott tube is inserted and attached to continuous suction, and the patient maintained on parenteral fluids. The vagina is prepared with a weak Lysol douche and a penicillin vaginal suppository inserted. Three to four liters of blood is cross-matched and made available for surgery. Parenteral barbiturates are administered the night prior to surgery. One hour prior to operation, the patient is given morphine ( $\frac{1}{8}$  grain in the majority of instances and atropine  $\frac{1}{100}$  grain). The Miller-Abbott tube is allowed to remain in situ.

Anesthesia is best administered by a competent medical anesthesiologist who has had experience in surgery of this magnitude. He is charged with governing the blood replacement so as not to permit marked drops in blood pressure as these may lead to fatal complications in patients of this age. Certainly, the patient is kept as calm and confident as possible prior to surgery. Thoughtless conversation contributing to traumatic psychic shock should be eliminated.

### **Type and Extent of Surgery**

The type and extent of surgery are determined by the degree of metastasis in the pelvis. Distant metastases, i.e., beyond the pelvis and usually involving the aortic nodes, make a hopeless prognosis. Inguinal or superficial and deep femoral metastatic nodes have been removed.

The decision to remove the bladder and rectum depends on whether or not they have been involved in the carcinomatous spread. Attempts at conservatism have led to later recurrence and further surgical steps are made more difficult because of the previous inadequate therapy. Lack of cystoscopic evidence of disease invading the bladder is no assurance that cells are not already in the tissues. To strip the bladder carefully from an invaded vaginal

tube and feel secure with this effort is wishful thinking. Is it not conceivable that as our experience increases we shall sacrifice the bladder and rectum more often, as this expedites the removal of the diseased tissues and gives greater assurance that we have the diseased areas most likely to be involved, bladder, rectum, ureters, and regional nodes, removed? The procedure of pelvic exenteration may be the answer to increasing our survivals in Stage III cases. We have witnessed the survival of one such patient for 6 years, in apparent adjustment to her situation with which she is well satisfied. Should the bladder be involved, it is removed and the ureters are transplanted to the sigmoid by a modified Coffey technique. Again in cases of rectal involvement, the bowel is resected and colostomy performed. If, following proctoscopy, however, the procedure is planned, the combined abdominoperineal approach is utilized. Of course, routine dissection of the primary nodes is accomplished (parametrial, paracervical, hypogastric, obturator, and external iliac). The sacral, inguinal, femoral, and common iliac nodes may be attacked but never above the bifurcation of the aorta. Here surgery is thorough and meticulous. The injection of lamp black into the the cervix prior to the procedure facilitates the dissection. Ureteral catheters are not used since they offer no technical advantage in the dissection.

During the procedure, one member of the team is assigned to the anesthesiologist to help with the task of maintaining the blood and electrolyte balance. This is done through cut-downs in the saphenous veins and facilities must be available for the administration of blood under pressure if the need arises.

### Postoperative Care

If success is to be achieved, postoperative care must be as thorough and efficient as the preoperative preparation and the surgery itself. The patient is given continuous oxygen via nasal catheter, fluids (blood and/or electrolytes) are given and observations made of blood pressure and pulse at ten-minute intervals until restlessness occurs. Readings are then taken on a thirty-minute basis until consciousness returns. From then on, hourly checks are made for the first twelve hours. Intake and output are accurately recorded though this is sometimes difficult in ureterosigmoid anastomoses. A rectal tube as a catheter sealed in the colostomy stoma and connected to a bottle serves to collect urinary specimens for various estimations. Frequent positional changes and early ambulation are mandatory, as is maintenance of body heat.

### Complications

*A. Anesthetic.*—In two instances in the series under tabulation at present, patients died at the onset of anesthesia during second-stage procedures.

Certainly, the responsibility for shock is divided in long procedures. The surgeon assumes responsibility for hemorrhage, trauma, and exposure with resultant loss of body heat. The anesthesiologist then must be watchful for oxygen deficiencies, overdosage of anesthetic agents, and airway obstructions. When either relaxes vigilance, the resulting disturbance in the patient's physiology may be fatal.



*B. Hemorrhage.*—This is the most frequently encountered complication in radical surgery. In most instances, this is immediate in that it occurs in the course of the procedure, the principal cause, of course, being the lack of cleavage planes produced by extension of disease or radiation fibrosis. In these instances, bleeding may reach exsanguinating proportions. For this reason, a member of the operative team is responsible for blood replacement. Needless to say, supplies are adequate and facilities for rapid replacement are available.

In one instance, we have noted a delayed exsanguinating hemorrhage. This occurred on the fourteenth postoperative day in a patient whose course to that time had been uneventful. In her case, direct extension into the right external iliac was noted at the time of surgery. At postmortem, a blow-out in this area of the external iliac vein was evident. Hypotensive methods of anesthesia are now being investigated and, as further experience is garnered, the method can be more fully evaluated.

*C. Shock.*—Certainly, the major contributing factors are hemorrhage and prolonged operating-anesthesia time, adding to the hypoxia which ultimately produces and sustains the shock state.

Prophylactically, the patient is maintained at optimum physiologic levels prior to surgery. Fluid, electrolyte, and hemoglobin values are maintained in surgery and in the immediate postoperative period. In two instances, a chronic shock state was encountered for a protracted period postoperatively. One lasted 3 days and the other almost 3 weeks. The latter case, at autopsy, showed chronic liver insufficiency and secondary biliary nephrosis.

*D. Urinary.*—Kidney complications in the form of pyelitis occurred frequently following both skin and sigmoid ureterostomies. In only one instance was there an inadequately treated pyelitis which was a major factor in the patient's downhill course.

One ureteral fistula has been encountered. Only through careful dissection and maintenance of the periurethral vascular anastomoses have damage and necrosis with subsequent fistula formation been avoided.

Vesicovaginal fistulas have occurred four times following combinations of radium and surgery, in instances where the bladder seemed free of disease. Devitalization of the muscularis by radiation and subsequent further trauma at surgery was sufficient to produce a fistula. These may be repaired from below as was one in the series, or in two instances an artificial bladder was created, using the vagina as a reservoir and a rubber plug to act in place of the urethral sphincter. Skin or sigmoid ureteral transplants may be utilized. Each case has its own exigencies and surgery of this nature is one of trial and improvisation.

"Neurogenic bladders" were encountered in four instances, i.e., bladders which remained atonic for long periods postoperatively, caused by a damaged nerve supply. The response to suction drainage and deflation was in each instance satisfactory.

*E. Hepatic.*—Hepatic complications arose in five instances. The onset of the disease was manifested by the early appearance (second to fourth day) of an ever-deepening jaundice. One patient died on the fourth, another on the

sixth, and the third on the twenty-first postoperative day. Autopsy findings showed consistently hepatic focal necrosis and biliary nephrosis. The combination of prolonged anesthesia, operative trauma, massive replacement of whole blood (no evidence of transfusion reaction, however) and shock were sufficient to overwhelm the liver in these instances.

In the fourth and fifth patients, a lower nephron syndrome complicated the picture, but both ultimately recovered uneventfully.

*F. Thrombophlebitis.*—This complicated the postoperative course in four instances, none of which ended fatally.

*G. Pulmonary.*—Complications arose in two of the three fatal hepatic complications. Likely these were, in the main, terminal.

*H. Intestinal.*—Rectovaginal fistula occurred in one instance due to radiation fibrosis. It was subsequently repaired and recurred.

Evisceration occurred twice and in both instances secondary closure was successful.

### Palliative Surgery

There were numerous instances of palliative surgery in which there was no attempt made to attack the primary disease. Operative procedures were performed for amelioration of the patient's discomfort: internal iliac ligation for the intractable hemorrhage, colostomy and ureteral transplantations for relief from fistulas produced by disease.

### Conclusion

Experience has taught us that not every patient with extensive cancer will be benefited by exenteration. The ideal patient is one without fixation, indicating that the malignant process has not invaded the fascia and muscles covering the bony girdle. In patients in whom either bladder or rectum is free of disease the urinary tract may be preserved intact if colostomy is necessary, or, if the bladder need be removed, the rectosigmoid can be kept intact and ureterocolic anastomosis performed. This often leads to later disappointment and if clinically the disease has extended within close proximity, removal of both bladder and rectum will add to the survival rate. Success or failure depends to a great degree on the general condition of the patient and that unknown factor, the resistance of the host to her tumor.

### Summary

1. After six years of observation, we believe that there is a definite place for pelvic exenteration, total or partial, in the treatment of carcinoma of the cervix found resistant to irradiation.

2. Evaluation of the patient's ability to withstand this surgery requires special knowledge of its extent and its impact on the human organism.

3. The preoperative preparation and postoperative care are as important as the operative technique and support during the surgery.

4. The complications of hemorrhage with resultant liver and pituitary necrosis, lower nephron nephrosis, and shock cause the majority of operative fatalities.

5. Palliative surgery lightens the discomfort of the patient with far-advanced cancer who has certain complications.

6. The pouch procedure of substitute bladder is most satisfactory. Colon implantation is next in our experience.

7. Surgery as extensive as is necessary for this problem requires special facilities and personnel if catastrophe is to be avoided.

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## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

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- American Gynecological Society.** (1876) *President*, Philip F. Williams. *Secretary*, John I. Brewer, 104 S. Michigan Ave., Chicago 3, Ill. Next meeting, Chateau Frontenac, Quebec, Canada, May 23, 24, and 25, 1955.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Herbert E. Schmitz, Chicago. *Secretary*, Frank R. Lock, Bowman Gray School of Medicine, Winston-Salem, N. C. Annual meeting at Hot Springs, Va., Sept. 9, 10, and 11, 1954.
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- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, Robert G. Nelson. *Secretary*, Charles H. Mauzy, Bowman Gray School of Medicine, Winston-Salem, N. C. Next meeting, Williamsburg Inn and Lodge, Williamsburg, Va., Feb. 10, 11, and 12, 1955.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Bernard J. Hanley, Los Angeles, Calif. *Secretary*, D. Frank Kaltreider, University Hospital, Baltimore 1, Md.
- Society of Obstetricians and Gynaecologists of Canada.** (1944) *President*, W. G. Cosbie, Toronto, Ont. *Secretary*, Robert B. Meiklejohn, Suite 334, Toronto Western Hospital, Toronto.
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- Akron Obstetrical and Gynecological Society.** (1946) *President*, Norman E. Wentsler. *Secretary*, Charles V. Bowen, Jr., 925 Second National Bldg., Akron 8. Meetings, third Friday of month, October, January, April, and July.
- Alabama Association of Obstetricians and Gynecologists.** (1940) *President*, J. C. Hope, Jr. *Secretary*, O. M. Otts, Jr., 1701 Springhill Ave., Mobile. Meetings, November and April.
- Alameda County Gynecological Society.** (1951) *President*, George F. Calvin. *Secretary*, Victor E. Koerper, 431 30th St., Oakland, Calif. Meetings, fourth Wednesday of each month.
- Arkansas Obstetrical and Gynecological Society.** (1953) *President*, Charles R. Wickard, Little Rock. *Secretary*, J. F. Kelsey, Fort Smith. Meetings, spring and fall.
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- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, R. Charles Nucci. *Secretary*, John C. Hughes, Schenley Apts., Pittsburgh 13, Pa. Meetings, first Monday, October through May, except January.

- Portland Society of Obstetricians and Gynecologists.** *President*, Kenneth J. Scales. *Secretary*, Gerald E. Kinzel, Medical Dental Bldg., Portland 5, Oregon. Meetings, fourth Wednesday, September through May.
- Queens Gynecological Society.** (1948) *President*, Daniel B. Langley. *Secretary*, Joseph A. Gaetane, 147-15 46th Ave., Flushing, N. Y. Meetings, second Wednesday, October, December, February, and April.
- Rochester Obstetrical and Gynecological Society.** (1939) *President*, Louis Iuppa. *Secretary*, Fred Fumia, 39 N. Goodman St., Rochester, N. Y. Meetings, September, December, March, and June.
- St. Louis Gynecological Society.** (1924) *President*, Willard M. Allen. *Secretary*, Eugene G. Hamilton, 8505 Delmar Blvd., St. Louis. Meetings, second Thursday, October, December, February, and April.
- San Antonio Obstetrical and Gynecological Society.** *President*, G. G. Passmore. *Secretary*, Frank M. Posey, Jr., 640 Moore Bldg. Meetings, first Monday of the month.
- San Diego Gynecological Society.** (1937) *President*, Ralph L. Hoffman. *Secretary*, George H. Derieux, 233 A St., San Diego, Calif. Meetings, second Monday of each month.
- San Francisco Gynecological Society.** (1929) *President*, James V. Campbell. *Secretary*, Edmund F. Anderson, 2445 Ocean Ave., San Francisco 27, Calif. Meetings second Friday, October through April.
- Seattle Gynecological Society.** (1941) *President*, Robert H. Stewart. *Secretary*, Charles S. Fine, 340 Stimson Bldg., Seattle 1, Wash. Meetings, third Wednesday of each month, except summer months.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, Frank B. C. Geibel. *Secretary*, Lawrence L. Hester, Jr., 16 Lucas St., Charleston. Meeting, spring.
- Southwest Obstetrical and Gynecological Society.** (1951) *President*, William Buster McGee. *Secretary*, Jesse A. Rust, Jr., 3115 University Ave., San Diego 4, Calif. Annual fall meeting, Sept. 10 and 11, 1954, Coronado Hotel, San Diego.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, G. F. Goff. *Secretary*, Carey Hiett, 815 Fifth Ave., Ft. Worth. Annual meeting in February.
- Utah Obstetrical and Gynecological Society.** (1948) *President*, M. S. Sanders. *Secretary*, Von G. Holbrook, 508 East South Temple, Salt Lake City 2. Meetings, to be announced.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Chester L. Riley. *Secretary*, Chester D. Bradley, 2914 West Ave., Newport News. Meetings, April and October.
- Washington Gynecological Society.** (1933) *President*, Raymond Holden. *Secretary*, James Dusbabek, 1801 K St., N. W., Washington, D. C. Meetings, October, December, January, March, and May.
- Washington State Obstetrical Association.** (1936) *President*, Richard R. Reekie. *Secretary*, Robert Campbell, 805 Medical Dental Bldg., Seattle 1. Next meeting, October 2, 1954, Washington Athletic Club, Seattle.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, George H. Stevens. *Secretary*, Dean D. Willson, 92 East Division St., Fond du Lac. Meetings, May and October.